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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES **PHS 2007-1**

SOLICITATION OF

THE PUBLIC HEALTH SERVICE

FOR

SMALL BUSINESS INNOVATION RESEARCH CONTRACT PROPOSALS

PROPOSAL RECEIPT DATE

NOVEMBER 6, 2006

Internet: http://grants.nih.gov/grants/funding/sbir.htm

TABLE OF CONTENTS

APPENDIX A — PROPOSAL COVER SHEET (MS Word | PDF) - USE FOR PHASE I PROPOSALS

APPENDIX B — ABSTRACT OF RESEARCH PLAN (MS Word | PDF) - USE FOR PHASE I, PHASE II, AND FAST-TRACK PROPOSALS

APPENDIX C — PRICING PROPOSAL (MS Word | PDF) - USE FOR PHASE I, PHASE II AND FAST-TRACK PROPOSALS

APPENDIX D — PHASE II TECHNICAL PROPOSAL COVER SHEET (MS Word | PDF) - USE FOR PHASE II AND FAST-TRACK PROPOSALS

APPENDIX E — STATEMENT OF WORK SAMPLE FORMAT (MS Word | PDF) - USE FOR PHASE II AND FAST-TRACK PROPOSALS

APPENDIX F — SUMMARY OF RELATED ACTIVITIES (MS Word | PDF) - USE FOR PHASE II AND FAST-TRACK PROPOSALS

APPENDIX G — PROPOSAL SUMMARY AND DATA RECORD (MS Word | PDF) - USE FOR PHASE II AND FAST-TRACK PROPOSALS

The Appendices noted above are in Microsoft Word and Adobe Acrobat Reader fillable format.

NOTE: Other software packages for completing these proposals may be available from other sources; however, it is essential that the type size and format specifications are met or the proposal may be returned without review.

DISCLAIMER: Reference to these software packages neither constitutes nor should be inferred to be an endorsement or recommendation of any product, service, or enterprise by the National Institutes of Health, any other agency of the United States Government, or any employee of the United States Government. No warranties are stated or implied.

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

SOLICITATION OF THE PUBLIC HEALTH SERVICE FOR SMALL BUSINESS INNOVATION RESEARCH (SBIR) CONTRACT PROPOSALS

I. GENERAL PROGRAM DESCRIPTION

The Small Business Innovation Research Program was reauthorized by the enactment of the Small Business Reauthorization Act of 2000, (Public Law 106-554) through Fiscal Year 2008. The authorizing SBIR legislation requires two significant programmatic changes:

- Commercialization Plan. All Phase II proposals must include a succinct commercialization plan. See instructions in *Section V.3*. for specific details.
- Data Collection Requirement. Each Phase II offeror will be required to provide information for the Small Business Administration (SBA) Tech-Net Database System. See SBA's Tech-Net website (http://tech-net.sba.gov/) for specific details.

The Public Health Service (PHS), Department of Health and Human Services (HHS), and certain other Federal agencies must reserve 2.5 percent of their current fiscal year extramural budgets for research or research and development (R/R&D) for a Small Business Innovation Research (SBIR) program. The objectives of the SBIR program include stimulating technological innovation in the private sector, strengthening the role of small business in meeting Federal R/R&D needs, increasing private sector commercialization of innovations developed through Federal SBIR R&D, increasing small business participation in Federal R&D, and fostering and encouraging participation by socially and economically disadvantaged small business concerns and women-owned small business concerns in the SBIR program.

The SBIR program consists of three separate phases:

Phase I: Feasibility
$100,000
6 months

The objective of Phase I is to determine the scientific or technical feasibility and commercial merit of the proposed research or R&D efforts and the quality of performance of the small business concern, prior to providing further Federal support in Phase II. Phase I awards normally may not exceed $100,000 for direct costs, indirect costs, and profit (fixed fee) for a period normally not to exceed 6 months.

Phase II: Full R/R&D Effort
$750,000
2 years

The objective of Phase II is to continue the research or R&D efforts initiated in Phase I. Funding shall be based on the results of Phase I and the scientific and technical merit and commercial potential of the Phase II proposal. Phase II awards normally may not exceed $750,000 for direct costs, indirect costs, and negotiated fees for a period normally not to exceed two years. That is, generally, a two-year Phase II project may not cost more than $750,000 for that project. *Phase II proposals may only be submitted upon the request of the Contracting Officer, if not submitted concurrently with the initial Phase I proposal under the Fast-Track procedure (described in Section V). Only one Phase II award may result from a single Phase I SBIR contract.*

Phase III: Commercialization stage without SBIR funds

The objective of Phase III, where appropriate, is for the small business concern to pursue with non-SBIR funds the commercialization objectives resulting from the outcomes of the research or R&D funded in Phases I and II. In some Federal agencies, Phase III may involve follow-on, non-SBIR funded R&D or production contracts for products or processes intended for use by the U.S. Government.

The competition for SBIR Phase I and Phase II awards satisfies any competition requirement of the Armed Services Procurement Act, the Federal Property and Administrative Services Act, and the competition in Contracting Act. Therefore, an agency that wishes to fund an SBIR Phase III project is not required to conduct another competition in order to satisfy those statutory provisions. As a result, in conducting actions relative to a Phase III SBIR award, it is sufficient to state for purposes of a Justification and Approval pursuant to FAR 6.302-5

that the project is a SBIR Phase III award that is derived from, extends, or logically concludes efforts performed under prior SBIR funding agreements and is authorized under 10 U.S.C. 2304(b)(2) or 41 U.S.C. 253(b)(2).

The NIH is interested in developing products and services via the SBIR program that would improve the health of the American people. In its commitment to also support President Bush's Executive Order 13329, encouraging innovation in manufacturing-related research and development, NIH will expand the focus of our SBIR/STTR program to encourage biomedical research related to advanced processing, manufacturing processes, equipment and systems; or manufacturing workforce skills and protection. This solicitation includes some topic areas that are considered relevant to manufacturing-related R&D. Additional information will be posted on the NIH SBIR/STTR website (http://grants.nih.gov/grants/funding/sbir.htm) and in the NIH Guide for Grants and Contracts as it becomes available. Small businesses may be interested in reading a U.S. Department of Commerce 2004 report, "Manufacturing in America: A Comprehensive Strategy to Address the Challenges to U.S. Manufacturers."

A. PURPOSE OF SOLICITATION

The purpose of this solicitation is to *invite Phase I contract proposals from small business* concerns that have the expertise to contribute to the mission of the awarding components identified below and to provide the opportunity for the submission of Phase II contract proposals concurrently with Phase I (see specific topics listed in Section XII and identified as accepting Fast-Track proposals).

Included are instructions for offerors to prepare contract proposals, a description of the proposal review process, and some conditions of a contract award. *Contract proposals will be accepted only if they respond specifically to a research topic within this solicitation (see* Section XII "Research Topics"*).* Otherwise, proposals will be returned to the offeror(s) without evaluation.

To apply for an SBIR grant rather than a contract, use the *Omnibus Solicitation of the Public Health Service for Small Business Innovation Research Grant Applications*. *(http://grants.nih.gov/grants/funding/sbir.htm#sol)*.

B. AWARDING COMPONENTS

The following awarding components of the PHS are participating in this SBIR Solicitation for Contract Proposals.

National Institutes of Health (NIH)

- National Cancer Institute (NCI)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- National Institute of Child Health and Human Development (NICHD)
- National Institute on Drug Abuse (NIDA)
- National Institute of Environmental Health Sciences (NIEHS)
- National Institute of Mental Health (NIMH)

Centers for Disease Control and Prevention (CDC)

- Immunization Safety Office (ISO)
- National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)
- National Center for HIV, STD, and TB Prevention (NCHSTP)
- National Center on Birth Defects and Developmental Disabilities (NCBDDD)

C. SBIR PROGRAM ELIGIBILITY

Organizational Criteria: Each organization submitting a proposal under the SBIR program must qualify as a small business concern (defined in Section III). In determining whether an offeror is a small business concern, an assessment will be made of several factors, including whether or not it is independently owned and operated and whether or not it is an affiliate of a larger organization whose employees, when added to those of the offeror organization, exceed 500. In conducting this assessment, all appropriate factors will be considered, including common ownership, common management, and contractual relationships.

In accordance with 13 C.F.R. 121.103, affiliation exists when "… one concern controls or has the power to control the other … control may be affirmative or negative, …it does not matter whether control is exercised, so long as the power to control exists." One of the circumstances that would lead to a finding that an organization is controlling or has the power to control another organization involves sharing common office space and/or employees and/or other facilities (e.g., laboratory space). 13 C.F.R. 121.103 also states that control or the power to control exists when "… key employees of one concern organize a new concern … and serve as its officers, directors, principal stockholders, and/or key employees; and one concern is furnishing or will furnish the other concern with subcontracts, financial or technical assistance, and/or other facilities, whether for a fee or otherwise."

Joint ventures and limited partnerships are eligible provided the entity created qualifies as a small business concern as defined in Section III of this solicitation.

Access to special facilities or equipment in another organization is permitted (as in cases where the SBIR awardee has entered into a subcontractual agreement with another institution for a specific, limited portion of the research project). However, *research space occupied by an SBIR contractor organization must be space that is available to and under the control of the SBIR contractor for the conduct of its portion of the project*. Where there is indication of sharing of common employees, a determination will be made on a case-by-case basis of whether or not such sharing constitutes control or the power to control.

Whenever a proposed SBIR project is to be conducted in facilities other than those of the offeror, a letter must be submitted *with* the proposal stating that leasing/rental arrangements have been negotiated for appropriate research space (i.e., space that will be available to and under the control of the SBIR contractor organization).

This letter must be signed by an *authorized official of the organization whose facilities are to be used for the SBIR project*. It also must include a description of the facilities and, if appropriate, equipment that will be leased/rented to the offeror organization.

All SBIR contract proposals will be reviewed with the above considerations in mind. *If it appears that an offeror does not meet eligibility requirements, the PHS will request an eligibility determination of the organization from the cognizant Small Business Administration (SBA) Government Contracting Area Office. The evaluation of the proposal for scientific merit will be deferred until the SBA provides a determination*.

Principal Investigator Criteria. The primary employment of the Principal Investigator must be with the offeror at the time of contract award and during the conduct of the proposed project. PHS policy defines a Principal Investigator as the single individual designated in the proposal with responsibility for the scientific and technical direction of the project. Primary employment means that *more than one half of the Principal Investigator's time* is spent in the employ of the small business concern. Employ means that more than one half of the Principal Investigator's salary and benefits are paid by the small business concern. *Primary employment with a small business concern precludes full-time employment at another organization*.

In the event that the Principal Investigator: (1) is a less-than-full-time employee of the small business, (2) is concurrently employed by another organization, or (3) gives the appearance of being concurrently employed by another organization, whether for a paid or unpaid position, at the time of submission of the proposal, *it is essential that documentation be submitted with the proposal to verify his/her eligibility*. If the Principal Investigator also is employed or appears to be employed by an organization other than the offeror (e.g., a university, a nonprofit research institute, or another company), a letter must be provided by the *non-offeror organization* confirming that the Principal Investigator will, if awarded an SBIR contract, become a less-than-half-time employee of such organization and will remain so for the duration of the SBIR project. If the Principal Investigator is employed by a university, the Dean's Office must provide such a letter. If the Principal Investigator is employed by another for-profit organization, the corporate official must sign the letter. This documentation is required for every proposal that is submitted, even one that is a revision of a previously submitted proposal.

Performance Site Criteria. For both Phase I and Phase II, the research or R&D project activity *must be performed in its entirety in the United States (see* Section III. Definitions*)*.

Market Research. *The PHS will not support any market research under its SBIR program*. Neither will it support studies of the literature that will lead to a new or expanded statement of work. Literature

searches where the commercial product is a database are acceptable. For purposes of the SBIR program, "market research" is the systematic gathering, recording, computing, and analyzing of data about problems relating to the sale and distribution of the subject of the research project. It includes various types of research, such as the size of potential market and potential sales volume, the identification of consumers most apt to purchase the products, and the advertising media most likely to stimulate their purchases. However, "market research" does not include activities under a research plan or protocol that require a survey of the public as part of the objective of the project to determine the impact of the subject of the research on the behavior of individuals.

II. AGENCY CONTACT FOR INFORMATION

Questions on the administration of an SBIR contract should be directed to the contracting officers listed in Section X. Contracting Officers and Addresses for Mailing and Delivery of Proposals.

Please direct questions of a general nature about the NIH SBIR program to:

Ms. Jo Anne Goodnight
NIH SBIR/STTR Program Coordinator
6705 Rockledge Drive
Rockledge I, Room 3540
Bethesda, MD 20892-7963
Phone: (301) 435-2688 Fax: (301) 480-0146
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The PHS SBIR Contract Solicitation ***is available in electronic format*** on the NIH "Small Business Funding Opportunities" home page at http://grants.nih.gov/grants/funding/sbir.htm#sol. The Table of Contents includes direct links and cross-references to specific sections of the document. Text searches in the PDF files are possible using the "binocular" icon. The Phase I and Phase II forms have been modified to enable the fields to be filled in directly using Microsoft Word, or Adobe Acrobat Reader software, which is free.

DISCLAIMER: Reference to these software packages neither constitutes nor should be inferred to be an endorsement or recommendation of any product, service, or enterprise by the National Institutes of Health, any other agency of the United States Government, or any employee of the United States Government. No warranties are stated or implied.

III. DEFINITIONS

Affiliate. This term has the same meaning as set forth in 13 C.F.R. Part 121 – Small Business Size Regulations, §121.103, *"How does the SBA determine affiliation?"*

Child. The NIH Policy on Inclusion of Children as Participants in Research Involving Human Subjects defines a child as an individual under the age of 21 years. The intent of the NIH policy is to provide the opportunity for children to participate in research studies when there is a sound scientific rationale for including them, and their participation benefits children and is appropriate under existing Federal guidelines. Thus, children must be included in NIH conducted or supported clinical research unless there are scientific and ethical reasons not to include them.

DHHS Regulations (45 C.F.R. Part 46, Subpart D, Sec.401-409) provide additional protections for children involved as subjects in research, based on this definition: "Children are persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted." Generally, state laws define what constitutes a "child." Consequently, the age at which a child's own consent is required and sufficient to participate in research will vary according to state law. For example, some states consider a person age 18 to be an adult and therefore one who can provide consent without parental permission.

Clinical Research. NIH defines human clinical research as: *(1)* Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and

cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies. *(2)* Epidemiologic and behavioral studies. *(3)* Outcomes research and health services research.

Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.

Clinical Trial. The NIH defines a clinical trial as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective.

Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial.

Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision making for the subject or the test itself imposes more than minimal risk for subjects.

Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

- *Phase I* clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).
- *Phase II* clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.
- *Phase III* studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.
- *Phase IV* studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.
- *NIH-Defined Phase III Clinical Trial*. For the purpose of the Guidelines, an NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Commercialization. The process of developing markets and producing and delivering products for sale (whether by the originating party or by others); as used here, commercialization includes both government and private sector markets.

Consultant. "Professional and consultant services," means those services rendered by persons who are members of a particular profession or possess a special skill and who are not officers or employees of the contractor. Examples include those services acquired by contractors or subcontractors in order to enhance their legal, economic, financial, or technical positions. Professional and consultant services are generally acquired to obtain information, advice, opinions, alternatives, conclusions, recommendations, training, or direct assistance, such as studies, analyses, evaluations, liaison with Government officials, or other forms of representation. See FAR 31.205-33, Professional and consultant service costs.

Contract. A mutually binding legal relationship obligating the seller to furnish the supplies or services (including construction) and the buyer to pay for them. It includes all types of commitments that obligate the Government to an expenditure of appropriated funds and that, except as otherwise authorized, are in writing. In addition to bilateral instruments, contracts include (but are not limited to) awards and notices of awards; job orders or task letters issued under basic ordering agreements; letter contracts; orders, such as purchase orders, under which the contract becomes effective by written acceptance or performance; and bilateral contract modifications. Contracts do not include grants and cooperative agreements covered by 31 U.S.C. 6301, et seq.

Essentially Equivalent Work. This term is meant to identify "scientific overlap," which occurs when: (1) substantially the same research is proposed for funding in more than one proposal (contract proposal or grant application) submitted to the same Federal agency; OR (2) substantially the same research is submitted to two or more different Federal agencies for review and funding consideration; OR (3) a specific research objective and the research design for accomplishing that objective are the same or closely related in two or more proposals or awards, regardless of the funding source.

Feasibility. The extent to which a study or project may be done practically and successfully.

Funding Agreement. Any grant, contract, or cooperative agreement entered into between any Federal agency and any small business concern for the performance of experimental, developmental, or research work, including products or services, funded in whole or in part by the Federal Government.

Human Subjects. 45 C.F.R.46, A living individual about whom an investigator (whether professional or student) obtains for research purposes (1) data through intervention or interaction with the individual, or (2) identifiable private information. The regulations governing the inclusion of human subjects in research extend to the use of human organs, tissues, and body fluids from individually identifiable human subjects as well as to graphic, written, or recorded information derived from individually identifiable human subjects.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

The use of autopsy materials is governed by applicable state and local law and is not directly regulated by 45 C.F.R. Part 46.

Innovation. Something new or improved, including research for: (1) development for new technologies, (2) refinement of existing technologies, or (3) development of new applications for existing technologies. For purposes of PHS programs, an example of "innovation" would be new medical or biological products, for improved value, efficiency, or costs.

Intellectual Property. The separate and distinct types of intangible property that are referred to collectively as "intellectual property," including but not limited to: patents, trademarks, copyrights, trade secrets, SBIR technical data (as defined in this section), ideas, designs, know-how, business, technical and research methods, and other types of intangible business assets, and including all types of intangible assets either proposed or generated by an SBC as a result of its participation in the SBIR program.

Joint Venture. A joint venture is an association of individuals and/or concerns with interests in any degree or proportion by way of contract, express or implied, consorting to engage in and carry out no more than three specific or limited-purpose business ventures for joint profit over a two year period, for which purpose they combine their efforts, property, money, skill, or knowledge, but not on a continuing or permanent basis for conducting business generally. This means that the joint venture entity cannot submit more than three offers over a two year period, starting from the date of the submission

of the first offer. A joint venture may or may not be in the form of a separate legal entity. The joint venture is viewed as a business entity in determining power to control its management.

A contractor and its ostensible subcontractor are treated as joint venturers, and therefore affiliates, for size determination purposes. An ostensible subcontractor is a subcontractor that performs primary and vital requirements of a contract, or of an order under a multiple award schedule contract, or a subcontractor upon which the prime contractor is unusually reliant. All aspects of the relationship between the prime and subcontractor are considered, including, but not limited to, the terms of the proposal (such as contract management, technical responsibilities, and the percentage of subcontracted work), agreements between the prime and subcontractor (such as bonding assistance or the teaming agreement), and whether the subcontractor is the incumbent contractor and is ineligible to submit a proposal because it exceeds the applicable size standard for that solicitation.

For size purposes, a concern must include in its total number of employees its proportionate share of joint venture employees.
http://www.sba.gov/library/cfrs/13cfr121.html

Key Personnel Engaged on Project. In addition to the Principal Investigator (PI), Key Personnel are defined as individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not salaries are requested.

Typically, these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level should be included if their involvement meets the definition of Key Personnel. *Consultants should also be included if they meet the same definition.*

Key Personnel must devote measurable effort to the project whether or not salaries are requested. "Zero percent" effort or “as needed” are not acceptable levels of involvement for those designated as Key Personnel.

Principal Investigator. The one individual designated by the offeror to direct the project or program to be supported by the contract. The Principal Investigator is responsible and accountable for the proper conduct of the project or program.

Prototype. A model of something to be further developed that includes designs, protocols, questionnaires, software, devices, etc.

Research or Research and Development (R/R&D). Any activity that is:

- A systematic, intensive study directed toward greater knowledge or understanding of the subject studied.
- A systematic study directed specifically toward applying new knowledge to meet a recognized need.
- A systematic application of knowledge toward the production of useful materials, devices, and systems or methods, including design, development, and improvement of prototypes and new processes to meet specific requirements.

SBIR Technical Data. All data generated during the performance of an SBIR award.

SBIR Technical Data Rights. The rights a small business concern obtains in data generated during the performance of any SBIR Phase I, Phase II, or Phase III award that an awardee delivers to the Government during or upon completion of a Federally-funded project, and to which the Government receives a license.

Small Business Concern. A small business concern is one that, at the time of award of Phase I and Phase II, meets *all* of the following criteria:

1. Is independently owned and operated, is not dominant in the field of operation in which it is proposing, has a place of business in the United States and operates primarily within the United States or makes a significant contribution to the US economy, and is organized for profit.
2. Is (a) at least 51% owned and controlled by one or more individuals who are citizens of, or permanent resident aliens in, the United States, or (b) for SBIR only, it must be a for-profit business concern that is at least 51% owned and controlled by another for-profit business concern that is at least 51% owned and controlled by one or more individuals who are citizens of, or permanent resident aliens in, the United States.

3. Has, including its affiliates, an average number of employees for the preceding 12 months not exceeding 500, and meets the other regulatory requirements found in 13 C.F.R. Part 121. Business concerns are generally considered to be affiliates of one another when either directly or indirectly, (a) one concern controls or has the power to control the other; or (b) a third-party/parties controls or has the power to control both.

Control can be exercised through common ownership, common management, and contractual relationships. The term "affiliates" is defined in greater detail in 13 C.F.R. 121.103. The term "number of employees" is defined in 13 C.F.R. 121.106.

A business concern may be in the form of an individual proprietorship, partnership, limited liability company, corporation, joint venture, association, trust, or cooperative. Further information may be obtained at http://sba.gov/size, or by contacting the Small Business Administration's Government Contracting Area Office or Office of Size Standards.

Socially and Economically Disadvantaged Individual. A member of any of the following groups: Black Americans; Hispanic Americans; Native Americans; Asian-Pacific Americans; Subcontinent Asian Americans; other groups designated from time to time by the Small Business Administration (SBA) to be socially disadvantaged; or any other individual found to be socially and economically disadvantaged by SBA pursuant to Section 8(a) of the Small Business Act, 15 U.S.C. 637(a).

Socially and Economically Disadvantaged Small Business Concern. A socially and economically disadvantaged small business concern is one that is at least 51% owned and controlled by one or more socially and economically disadvantaged individuals, or an Indian tribe, including Alaska Native Corporations (ANCs), a Native Hawaiian Organization (NHO), or a Community Development Corporation (CDC). Control includes both the strategic planning (as that exercised by boards of directors) and the day-to-day management and administration of business operations. See 13 C.F.R. 124.109, 124.110, and 124.111 for special rules pertaining to concerns owned by Indian tribes (including ANCs), NHOs or CDCs, respectively.

Subcontract. Any agreement, other than one involving an employer-employee relationship, entered into by a Federal Government prime contractor calling for supplies or services required solely for the performance of the prime contract or another subcontract.

United States. The 50 states, the territories and possessions of the Federal Government, the Commonwealth of Puerto Rico, the District of Columbia, the Republic of the Marshall Islands, the Federated States of Micronesia, and the Republic of Palau.

Women-Owned Small Business Concern. A small business concern that is at least 51% owned by one or more women, or in the case of any publicly owned business, at least 51% of the stock is owned by women, and women control the management and daily business operations.

IV. PHASE I PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

A. LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase I proposals must not exceed 25 single-sided, single-spaced pages, including the cover sheet, abstract, cost breakdown, and all enclosures or attachments. Pages should be of standard size (8 l/2" X 11"), and you should use an Arial, Helvetica, Palatino Linotype or Georgia typeface and a font size of 11 points or larger. Excluded from the 25-pages are cover letters, Human Subjects Research and Vertebrate Animal information, letters of commitment from collaborators and consultants and letters to determine eligibility. Unless specifically solicited by a Contracting Officer, no other appendices or attachments may be submitted, and if submitted, they will not be considered in the evaluation of scientific and technical merit. Proposals in excess of the page limitation shall not be considered for review or award.

B. PROPOSAL COVER SHEET

Complete the form identified as Appendix A (MS Word | PDF), and use it as the first page of the proposal. *No other cover sheet should be used*.

- ***Topic Number.*** Provide the appropriate numerical designator of the research topic for which your proposal is being submitted. If your proposal is responsive to a subtopic, provide both the topic and subtopic numbers. (A numerical or alphabetical designator precedes each topic and subtopic.)

- ***Project Title.*** Select a title that reflects the substance of the project. Do not use the title of the topic that appears in the solicitation.

C. ABSTRACT OF RESEARCH PLAN

Complete the form identified as Appendix B (MS Word | PDF), and insert it as the second page of each proposal. Abstracts of successful proposals will be published by NIH and, therefore, should not contain proprietary information. The abstract should include a brief description of the problem or opportunity, specific aims, and a description of the effort. Summarize anticipated results and potential commercial applications of the proposed research.

D. RESEARCH PLAN

Any research proposal involving the collection of information, such as surveys or interviews, of 10 or more public respondents will require clearance by the U.S. Office of Management and Budget. Therefore, it is not practical to propose such an activity for Phase I, which normally has only a six-month duration.

Beginning on page three of the proposal, discuss in the order indicated the following elements:

1. ***Identification and Significance of the Problem or Opportunity.*** Provide a clear statement of the specific technical problem or opportunity addressed.

2. ***Technical Objectives.*** State the specific objectives of the Phase I effort, including the technical questions it will try to answer to determine the feasibility of the proposed approach.

3. ***Work Plan.*** Provide a detailed plan for the R&D to be carried out, including the experimental design, procedures, and protocols to be used. Address the objectives and the questions stated in *Item 2* above. Discuss in detail the methods to be used to achieve each objective or task. For specific guidance and instructions related to Human Subjects research, please see the section entitled, "Human Subjects Research and Protection from Risk" and the "Human Subjects Research Guidance and Information Supplement."

4. ***Related Research or R&D.*** Describe significant research or R&D that is directly related to the proposal, including any conducted by the Principal Investigator/Project Manager or by the proposing firm. Describe how it relates to the proposed effort and any planned coordination with outside sources. *The Principal Investigator/Project Manager must persuade reviewers of his or her awareness of recent significant research or R&D conducted by others in the same scientific field*.

5. ***Relationship with Future R&D.***

   a. State the results expected from the proposed approach.

   b. Discuss the significance of the Phase I effort in providing a foundation for the Phase II R/R&D effort.

6. ***Potential Commercial Applications.*** Describe why the proposed project appears to have potential commercial applications, and whether and by what means the proposed project appears to have potential use by the Federal Government.

7. ***Key Personnel and Bibliography of Directly Related Work.*** Identify key personnel, including their directly related education, experience, and bibliographic information. Where resumes are extensive, focus on summaries of the most relevant experience or publications. *Provide dates and places of employment* and some information about the nature of each position or professional experience. Resumes must identify the current or most recent position.

8. ***Consultants.*** Involvement of consultants in the planning and/or research stages of the project is permitted. However, such use must be described in detail and supported by appropriate letters from each individual confirming his/her role in the project.

9. ***Facilities and Equipment.*** Indicate where the proposed research will be conducted. *One of the performance sites must be the offeror organization*. Describe the facilities to be used; identify the location; and briefly indicate their capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Include clinical, computer, and office

facilities of the offeror and those of any other performance sites to be used in the project.

List the most important equipment items already available for this project, noting location and pertinent capabilities of each.

Any equipment and products purchased with Government funds shall be American-made, to the extent possible.

Title to Equipment. Title to equipment purchased with Government funding by the SBIR awardee in relation to project performance vests upon acquisition in the Federal Government. However, the Government may transfer such title to an SBIR awardee upon expiration of the project where the transfer would be more cost-effective than recovery of the property.

E. CURRENT AWARDS AND PENDING PROPOSALS/APPLICATIONS

As the PHS uses both contracts and grants in its SBIR program, a small business concern may not submit both a contract proposal and a grant application for essentially the same project to the same or different awarding component(s) of the PHS. The only exception would be the submission of a grant application after a contract proposal has been evaluated and is no longer being considered for award. A firm that receives a Phase I SBIR contract may be solicited to submit a Phase II grant application and vice versa.

While it is permissible, with proposal notification, to submit identical proposals or proposals containing a significant amount of essentially equivalent work (as defined in this solicitation) for consideration under numerous Federal program solicitations, it is unlawful to enter into contracts or grants requiring essentially equivalent effort.

If there is any question concerning this, it must be disclosed to the soliciting agency or agencies before award.

If a firm elects to submit identical proposals or proposals containing a significant amount of essentially equivalent work under other Federal program solicitations, include a statement in each such proposal indicating the information requested in items 1-10 set forth below.

In addition, provide the information requested in items 1-10 on (a) active funding through contracts, grants, and cooperative agreements from public or private sponsors; (b) contract proposals and grant and cooperative agreement applications pending review or funding; and (c) contract proposals and grant and cooperative agreement applications about to be submitted.

1. Name and address of the funding source.
2. Type of award (contract, grant, cooperative agreement) and identifying number.
3. Title of research project.
4. Name and title of Principal Investigator or Project Manager.
5. Hours per week on the project by the Principal Investigator or Project Manager.
6. Annual costs proposed or awarded.
7. Entire period of support.
8. Date of proposal/application submission or date of award.
9. Title, number, and date of solicitations under which proposals or applications were submitted or awards received.
10. The specific applicable research topic for each SBIR proposal or application submitted or award received. *Specifically identify those projects that are SBIR*.

F. PRIOR SBIR PHASE II AWARDS

If the small business concern has received more than 15 Phase II awards in the prior 5 fiscal years, submit name of awarding agency, date of award, funding agreement number, amount, topic or subtopic title, follow-on agreement amount, source, and date of commitment and current commercialization status for each Phase II. This required proposal information will not be counted toward the proposal page limitations.

G. PROPOSED COST BREAKDOWN

Complete the form identified as Appendix C (Contract Pricing Proposal) (MS Word | PDF). The cost breakdown should appear as the last section of the proposal. *If some items on this form do not apply to the proposed project, they need not be completed*.

- Under “Government Solicitation No.,” enter “PHS 2007-1.”

- If supplies are proposed, provide the quantities and the price per unit.
- Under "Direct Labor," *list all key personnel by name*. Support personnel may be consolidated into categories or labor classes, e.g., research assistants or data processing clerks.
- If travel is proposed, provide the following details on "Exhibit A – Supporting Schedule": destination(s); duration of trip(s); number of travelers; and cost per trip, broken down by cost elements, e.g., airfare, lodging, and meals.
- If consultants are proposed, provide name(s), rate(s), and number of hours/days.
- If a subcontract is proposed, provide the same type of detailed cost breakdown as required for Appendix C. *Also provide a copy of the subcontractual agreement*.
- Use "Exhibit A – Supporting Schedule" to itemize and justify all major cost elements. If more space is needed, use Page 3 of Appendix C.
- *Normally, at least two-thirds or 67% of the entire research or analytical effort must be carried out by the offeror*, i.e., subcontracts for portions of the scientific/technical effort and consultant fees normally may not exceed 33% of the total cost breakdown.

H. STREAMLINING THE CONTRACTING PROCESS

With the Federal Acquisition Streamlining Act of 1994 and the Federal Acquisition Reform Act of 1996, a number of terms and conditions that previously applied to contracts under $100,000 are no longer applicable. Under the SBIR program, Phase I awards, which normally may not exceed $100,000, will reflect the streamlined contract document.

The NIH has initiated special *"just in time" procedures* that are designed to reduce the administrative burden on offerors without compromising the information needed during the initial evaluation of proposals. Certain documents that would previously have been required for submission with the Phase II proposal will be requested at a later stage in the evaluation process. The following documentation is part of the "just in time" procedures and offerors who elect to submit proposals under the *"Fast-Track" initiative* below are not required to submit this documentation with their initial Phase II business proposal:

- ***Travel Policy.*** The offeror's written travel policy.
- ***Annual Financial Report.*** The offeror's most recent annual financial report.
- ***Total Compensation Plan.*** Salary and fringe benefits of professional employees under service contracts.
- ***Data Substantiating the Costs and Prices Proposed.*** That is, payroll documentation, vendor quotes, invoice prices, etc.

I. REQUIREMENT FOR ADEQUATE ASSURANCE OF PROTECTION OF HUMAN SUBJECTS

The HHS regulations for the Protection of Human Subjects, 45 C.F.R. 46 (as amended), provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the HHS. *The requirement is that an approved assurance of compliance with the regulations must be on file with the Office for Human Research Protections (OHRP), DHHS (*http://www.hhs.gov/ohrp*) before an HHS award can be made.*

Neither an Institutional Review Board (IRB) review nor an OHRP-approved Assurance is required at the time the proposal is submitted or at the time that the proposals are peer reviewed.

Human Subjects Research and Protection from Risk

This information must be submitted with the proposal, but is excluded from the 25-page limitation.

Provided below is a table that presents six possible research scenarios, and links to the instructions for providing information on human subjects protection information and the inclusion of women, minorities, and children specific to each scenario. All research will fall into one of these six scenarios. Which scenario best matches your proposed research depends on your answers to the following five questions:

Question 1: Does your proposed research involve human subjects?

Question 2: Does your proposed human subjects research meet the criteria for one or more of the exemptions in the HHS regulations (45 C.F.R. 46)?

Question 3: Does your proposed research meet the definition of clinical research?

Question 4: Does your proposed research include a clinical trial?

Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

If you answer "Yes" to any of the five questions, proceed to the table below, select the scenario that best matches your responses and then follow the instructions located on the scenario pages.

If you need additional guidance then click on the questions or the column heading in the table below and you will be provided additional information and guidance.

Much of the information on the protection of human subjects that you are required to provide in this section is identical to information that will be required for IRB review.

DECISION TABLE FOR HUMAN SUBJECTS RESEARCH, PROTECTION AND THE INCLUSION OF WOMEN, MINORITIES, AND CHILDREN

	Criteria and Answers to Questions 1 thru 5				
Scenarios with linked instructions	1. Human Subjects Research	2. Exempt from HHS Human Subjects Regulations	3. Clinical Research	4. Clinical Trial	5. NIH-Defined Phase III Clinical Trial
A No Human Subjects	No	N/A	N/A	N/A	N/A
Requirements for Scenario A: If Human Subjects is "Yes," see Scenarios B-F below.					
B Human Subjects/E-4	Yes	Yes Exemption: 4	No	N/A	N/A
Requirements for Scenario B: - Indicate Exemption 4 (E-4) and include justification that E-4 is appropriate.					
C Human Subjects/ Other Exemptions	Yes	Yes Exemptions: 1, 2, 3, 5, 6	Yes	N/A	N/A
Requirements for Scenario C: - Indicate Exemption number(s) and include justification that the designated exemption(s) is appropriate. - Address "Inclusion of Women and Minorities" - Address "Inclusion of Children"					
D Clinical Research	Yes	No	Yes	No	N/A
Requirements for Scenario D: - Address Protection of Human Subjects - Address "Inclusion of Women and Minorities" - Address "Inclusion of Children" "Targeted/Planned Enrollment Table(s)" for each new study/ protocol (New proposals; Competing Continuation proposals; Competing Supplements) - "Inclusion Enrollment Report Table(s)" (Competing Continuations; Competing Supplements)					
E Clinical Trials	Yes	No	Yes	Yes	No
Requirements for Scenario E: - All requirements in Scenario D - Data and Safety Monitoring Plan - Note: Some trials may require a Data and Safety Monitoring Board, based on risk					
F NIH-Defined Phase III Clinical Trial	Yes	No	Yes	Yes	Yes
Requirements for Scenario F: - All requirements in Scenario E Increased requirements for Inclusion of Women and Minorities in Clinical Research					

J. REQUIREMENT FOR ADEQUATE ASSURANCE OF COMPLIANCE WITH THE PHS POLICY ON HUMANE CARE AND USE OF LABORATORY ANIMALS

Instructions and Required Information

This information must be submitted with the proposal, but is excluded from the 25-page limitation.

Create a section heading entitled **"Vertebrate Animals."** Place it immediately following the "Research Plan" section of the proposal (or after Human Subjects Research section, if applicable).

Under the Vertebrate Animals heading, address the following five points. In addition, when research involving vertebrate animals will take place at collaborating site(s) or other performance site(s), provide this information before discussing the five points. Although no specific page limitation applies to this section of the proposal, be succinct.

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Design and Methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.
2. Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.
3. Provide information on the veterinary care of the animals involved.
4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.
5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations.

Guidance and Additional Instructions

NIH no longer requires Institutional Animal Care and Use Committee approval of the proposed research before NIH peer review of a proposal (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-064.html).

In August, 2002 NIH announced an IACUC "just-in-time" process for applications submitted for the October 1, 2002 deadline or other deadlines where the applications had a May/June 2003 Council review. The PHS policy requirement that no award may be made without an approved Assurance and without verification of IACUC approval remains in effect. The new policy gave institutions flexibility in the timing of IACUC review relative to the submission of a proposal and the verification of IACUC review. The policy does not require that IACUC approval be deferred. Institutional officials retain the discretion to require IACUC approval prior to NIH peer review in circumstances of their choosing if deemed necessary. As part of the NIH peer review process, the scientific review group will continue to address the adequacy of animal usage and protections in the review of a proposal and will continue to raise any concerns about animal welfare issues. Verification of IACUC approval will be required in a "just-in-time" fashion prior to award.

The PHS *Policy on Humane Care and Use of Laboratory Animals* requires that offeror organizations proposing to use vertebrate animals file a written Animal Welfare Assurance with the Office of Laboratory Animal Welfare (OLAW), establishing appropriate policies and procedures to ensure the humane care and use of live vertebrate animals involved in research activities supported by the PHS. The PHS policy stipulates that an offeror organization, whether domestic or foreign, bears responsibility for the humane care and use of animals in PHS-supported research activities. This policy implements and supplements the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* and requires that institutions use the *Guide for the Care and Use of Laboratory Animals* as a basis for developing and implementing an institutional animal care and use program. This policy does not affect applicable state or local laws or regulations that impose more stringent standards for the care and use of laboratory animals. All institutions are required to comply, as applicable, with the Animal Welfare Act as amended (7 USC 2131 et sec.) and other Federal statutes and regulations relating to animals. These documents

are available from the Office of Laboratory Animal Welfare, National Institutes of Health, Bethesda, MD 20892, (301) 496-7163.

The PHS Policy defines “animal” as “any live, vertebrate animal used or intended for use in research, research training, experimentation or biological testing or for related purposes.”

No PHS award for research involving vertebrate animals will be made to an offeror organization unless that organization is operating in accordance with an approved Animal Welfare Assurance and provides verification that the IACUC has reviewed and approved the proposed activity in accordance with the PHS policy. Proposals may be referred by the PHS back to the IACUC for further review in the case of apparent or potential violations of the PHS policy. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the PHS policy. Foreign offeror organizations applying for PHS awards for activities involving vertebrate animals are required to comply with PHS policy or provide evidence that acceptable standards for the humane care and use of animals will be met.

K. LIMITATIONS ON USE OF APPROPRIATED FUNDS

The Department of Health and Human Services Appropriations Act, 2006 (Public Law 109-149), limits the use of appropriated funds on NIH grant, cooperative agreement, and contract awards for Fiscal Year 2006, as specified below. It is anticipated that these limitations will continue in subsequent fiscal years.

Salary Rate Limitation

Public Law 109-149 restricts the use of Federal funds to pay the direct salary of an individual under an NIH grant, cooperative agreement, or applicable contract, at a rate in excess of Executive Schedule, Level I. The salary rate limitation also applies to individuals proposed under subcontracts; however, it does not apply to consultants. The legislation also does not apply to firm-fixed-price contracts. Effective January 1, 2006, the Executive Level I salary is $183,500 per year.

Anti-Lobbying (for contracts exceeding $100,000)

"(a) No part of any appropriation contained in this Act shall be used, other than for normal and recognized executive-legislative relationships, for publicity or propaganda purposes, for the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television, or video presentation designed to support or defeat legislation pending before the Congress or any State legislature, except in presentation to the Congress or any State legislature itself. (b) No part of any appropriation contained in this Act shall be used to pay the salary or expenses of any grant or contract recipient, or agent acting for such recipient, related to any activity designed to influence legislation or appropriations pending before the Congress or any State legislature."

Restriction on Distribution of Sterile Needles

"Notwithstanding any other provision of this Act, no funds appropriated under this Act shall be used to carry out any program of distributing sterile needles or syringes for the hypodermic injection of any illegal drug."

Acknowledgment of Federal Funding

"When issuing statements, press releases, requests for proposals, bid solicitations and other documents describing projects or programs funded in whole or in part with Federal money, all grantees receiving Federal funds included in this Act, including but not limited to State and local governments and recipients of Federal research grants, shall clearly state: (1) the percentage of the total costs of the program or project which will be financed with Federal money; (2) the dollar amount of Federal funds for the project or program; and (3) percentage and dollar amount of the total costs of the project or program that will be financed by non-governmental sources."

Restriction on Abortions

“(a) None of the funds appropriated under this Act, and none of the funds in any trust fund to which funds are appropriated in this Act, shall be expended for any abortion.”

Ban on Funding of Human Embryo Research

“(a) None of the funds made available in this Act may be used for: (1) the creation of a human embryo or embryos for research purposes; or (2) research in

which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) (2) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). (b) For purposes of this section, the term "human embryo or embryos" includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells."

Limitation on Use of Funds for Promotion of Legalization of Controlled Substances

"(a) None of the funds made available in this Act may be used for any activity that promotes the legalization of any drug or other substance included in schedule I of the schedules of controlled substances established by section 202 of the Controlled Substances Act (21 U.S.C.812). (b) The limitation in subsection (a) shall not apply when there is significant medical evidence of a therapeutic advantage to the use of such drug or other substance or that federally sponsored clinical trials are being conducted to determine therapeutic advantage."

V. "FAST-TRACK" INITIATIVE

(Applicable Only to Proposals Submitted to NIH)

The "Fast-Track" initiative is a parallel review option available to those small business concerns (offeror organizations) whose proposals satisfy additional criteria that enhance the probability of the project's commercial success. This initiative is applicable only to NIH and only if an awarding component indicates it is accepting Fast-Track proposals for a particular topic. (Refer to Section XII, "Research Topics," for notation.)

The Fast-Track initiative is an opportunity for small business concerns to submit both a Phase I and Phase II proposal for concurrent peer review. This initiative also has the potential to minimize any funding gap between Phase I and Phase II.

Fast-Track Proposal Process

To identify the proposals as Fast-Track, check the box marked "Yes" next to the words "Fast-Track Proposal" shown on the Phase I Proposal Cover Sheet, Appendix A (MS Word | PDF).

The small business concern must submit both a Phase I and a Phase II proposal for concurrent initial peer review and evaluation. The Fast-Track proposal must consist of the following parts:

1. ***Phase I Proposal.*** Prepared in accordance with Section IV. Phase I Proposal Preparation Instructions and Requirements, and addressing all factors stated in the evaluation criteria (Section VII) for Phase I proposals.
2. ***Phase II Proposal.*** Prepared in accordance with Section VI, Fast-Track Phase II Proposal Preparation Instructions and Requirements and addressing all factors stated in the evaluation criteria (Section VII) for Phase II proposals.
3. **Commercialization Plan**

(*Applicable to all Phase II proposals and Phase I/ Phase II Fast-Track proposals*.)

All Phase II proposals *and* Fast-Track proposals must include a succinct Commercialization Plan. The Commercialization Plan is limited to *15 pages*. Be succinct. There is no requirement for offerors to use the maximum allowable pages allotted to the Commercialization Plan.

Create a section entitled, "Commercialization Plan," and provide a description in each of the following areas:

a. ***Value of the SBIR Project, Expected Outcomes, and Impact.*** Describe, in layperson's terms, the proposed project and its key technology objectives. Clarify the need addressed, specifying weaknesses in the current approaches to meet this need. In addition, describe the commercial applications of the research and the innovation inherent in this proposal. Be sure to also specify the potential societal, educational, and scientific benefits of this work. Explain the non-commercial impacts to the overall significance of the project. Explain how the SBIR project integrates with the overall business plan of the company.

b. ***Company.*** Give a brief description of your company including corporate objectives, core competencies, present size (annual sales level and number and types of employees), history of previous Federal and non-Federal funding, regulatory experience, and subsequent commercialization, and any current products/services that have significant sales.

Include a short description of the origins of the company. Indicate your vision for the future, how you will grow/maintain a sustainable business entity, and how you will meet critical management functions as your company evolves from a small technology R&D business to a successful commercial entity.

c. ***Market, Customer, and Competition.*** Describe the market and/or market segments you are targeting and provide a brief profile of the potential customer. Tell what significant advantages your innovation will bring to the market, e.g., better performance, lower cost, faster, more efficient or effective, new capability. Explain the hurdles you will have to overcome in order to gain market/customer acceptance of your innovation.

Describe any strategic alliances, partnerships, or licensing agreements you have in place to get FDA approval (if required) and to market and sell your product.

Briefly describe your marketing and sales strategy. Give an overview of the current competitive landscape and any potential competitors over the next several years. (*It is very important that you understand and know the competition*.)

d. ***Intellectual Property (IP) Protection.*** Describe how you are going to protect the IP that results from your innovation. Also note other actions you may consider taking that will constitute at least a temporal barrier to others aiming to provide a solution similar to yours.

e. ***Finance Plan.*** Describe the necessary financing you will require, and when it will be required, as well as your plans to raise the requisite financing to launch your innovation into Phase III and begin the revenue stream. Plans for this financing stage may be demonstrated in one or more of the following ways:

- Letter of commitment of funding.
- Letter of intent or evidence of negotiations to provide funding, should the Phase II project be successful and the market need still exist.
- Letter of support for the project and/or some in-kind commitment, e.g., to test or evaluate the innovation.
- Specific steps you are going to take to secure Phase III funding.

f. ***Production and Marketing Plan.*** Describe how the production of your product/service will occur (e.g., in-house manufacturing, contract manufacturing). Describe the steps you will take to market and sell your product/service. For example, explain plans for licensing, internet sales, etc.

g. ***Revenue Stream.*** Explain how you plan to generate a revenue stream for your company should this project be a success. Examples of revenue stream generation include, but are not limited to, manufacture and direct sales, sales through value added resellers or other distributors, joint venture, licensing, service. Describe how your staffing will change to meet your revenue expectations.

Offerors are *encouraged to seek commitment(s) of funds and/or resources from an investor or partner organization for commercialization* of the product(s) or service(s) resulting from the SBIR contract.

Your Phase III funding may be from any of a number of different sources including, but not limited to: SBIR firm itself; private investors or “angels”; venture capital firms; investment companies; joint ventures; R&D limited partnerships; strategic alliances; research contracts; sales of prototypes (built as part of this project); public offering; state finance programs; non SBIR-funded R&D or production commitments from a Federal agency with the intention that the results will be used by the United States government; or other industrial firms.

Fast-Track proposals that do not contain all parts described above will be redirected for Phase I consideration only.

The Phase I and Phase II proposals will be scored individually.

Fast-Track Phase II proposals may be funded following submission of the Phase I final report, and a determination that the Phase I objectives were met, feasibility was demonstrated, and funds are available.

VI. FAST-TRACK PHASE II PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

A. LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase II proposals generally should not exceed a total of 150 single-spaced pages, including all enclosures and attachments. Pages should be of standard size (8 1/2" x 11") and you should use an Arial, Helvetica, Palatino Linotype or Georgia typeface and a font size of 11 points or larger. Excluded from the page limitation are cover letters and letters from collaborators and consultants.

B. TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Phase II Technical Proposal Cover Sheet** - Use Appendix D (MS Word | PDF).
2. **Table of Contents**
3. **Abstract of the Research Plan** - Use Appendix B (MS Word | PDF). State the broad, long-term objectives and specific aims. Do not include any proprietary information. Briefly and concisely describe the research design and methods for achieving these goals.
4. **Anticipated Results of Phase I Effort** - Briefly discuss and summarize the objectives of your Phase I effort, the research activities to be carried out, and the anticipated results.
5. **Research Plan**

   a. *Detailed Approach and Methodology* - provide an explicit detailed description of the Phase II approach. This section should be the major portion of the proposal and must clearly show advancement in the project appropriate for Phase II. Indicate not only what is planned, but also how and where the work will be carried out. List all tasks in a logical sequence to precisely describe what is expected of the contractor in performance of the work. Tasks should contain detail to (1) establish parameters for the project; (2) keep the effort focused on meeting the objectives; (3) describe end products and deliverables; and (4) describe periodic/final reports required to monitor work progress under the contract. Offerors using Human Subjects or Vertebrate Animals in their research should refer to the specific instructions provided in this solicitation.

   b. *Personnel* - List by name, title, department and organization, the extent of commitment to this Phase II effort, and detail each person's qualifications and role in the project. *Provide resumes for all key staff members,* describing directly related education, experience, and relevant publications. Describe in detail any involvement of subcontractors or consultants, and *provide resumes for all key subcontractor staff. Also, include letters of commitment with proposed consultants confirming the extent of involvement and hourly/daily rate.*

   c. *Resources* - List/describe all equipment, facilities and other resources available for this project, including the offeror's clinical, computer and office facilities/equipment at any other performance site that will be involved in this project. Briefly state their capacities, relative proximity and extent of availability to this effort. *(Any equipment specifically proposed as a cost to the contract must be justified in this section as well as detailed in the budget. Equipment and products purchased with Government funds shall be American-made, to the extent possible. Title to the equipment will vest in the Government.)*

   d. *Other considerations* - Provide a brief narrative of any unique arrangements, safety procedures in place, animal welfare issues, human subjects, etc. Note: If the research plan includes the use of human subjects or animals, refer to paragraphs IV. I-K of this solicitation for further guidance.

   e. *Appendices*

      (1) **Work Statement** – The Contracting Officer may require the offeror to develop a Statement of Work similar in format to the sample in Appendix E (MS Word | PDF). Create this from your detailed approach and methodology. It will be incorporated into the final contract document. Do not include proprietary information.

      (2) **Commercialization Plan** – Required for ALL Phase II and Fast-Track proposals. Comply with requirements referred to in *Section V.3.*

6. **Summary of Related Activities** - Use Appendix F (MS Word | PDF).
7. **Technical Proposal Cost Information** - Use Appendix C (MS Word | PDF). Delete the fringe benefit costs, indirect costs and fee. Prepare a separate Appendix C for each year of the contract and a summary of the entire project.
8. **Number of Copies** - Submit an original and 9 copies.

C. BUSINESS PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Cover Page** - Use NIH Form 2043, Proposal Summary and Data Record, Appendix G (MS Word | PDF).
2. **Proposed Cost Breakdown** - Use Appendix C (MS Word | PDF). Explain the basis for all costs and submit documentation to support all proposed costs. Prepare a separate Appendix C for each year of the contract and a summary of the entire project.
3. **Number of Copies** - Submit an original and 4 copies.

VII. METHOD OF SELECTION AND EVALUATION CRITERIA

All Phase I and II proposals will be evaluated and judged on a competitive basis. Using the technical evaluation criteria in Section VII.B., a panel of scientists, consisting primarily of nongovernment experts knowledgeable in the disciplines or fields under review, will evaluate proposals to determine the most promising technical and scientific approaches. Each proposal will be judged on its own merit. The Agency is under no obligation to fund any proposal or any specific number of proposals in a given topic. It also may elect to fund several or none of the proposed approaches to the same topic or subtopic.

A. EVALUATION PROCESS

Your proposal will be peer reviewed by a panel of scientists selected for their competence in relevant scientific and technical fields. Each peer review panel will be responsible for evaluating proposals for scientific and technical merit. The peer review panel provides a rating, makes specific recommendations related to the scope, direction and/or conduct of the proposed research, and for those proposals recommended for award, may provide a commentary about the funding level, labor mix, duration of the proposed contract project, vertebrate animal and human subject research issues. The Institute program staff of the awarding component will conduct a second level of review. Recommendations of the peer review panel and program staff are based on judgments about not only the technical merit of the proposed research but also its relevance and potential contributions to the mission and programs of the awarding component. A Phase I or Phase II contract may be awarded only if the corresponding proposal has been recommended as technically acceptable by the peer review panel. *Funding for any/all acceptable proposals is not guaranteed.*

B. TECHNICAL EVALUATION CRITERIA

In considering the technical merit of each proposal, the following factors will be assessed:

FACTORS FOR PHASE I PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach and identification of clear measurable goals (milestones) to be achieved during Phase I. (*Preliminary data are not required for Phase I proposals*.)	40%
2. The qualifications of the proposed Principal Investigator, supporting staff, and consultants.	20%
3. The potential of the proposed research for technological innovation.	15%
4. The potential of the proposed research for commercial application.	15%
5. The adequacy and suitability of the facilities and research environment.	10%

FACTORS FOR PHASE II PROPOSALS	WEIGHT
1. The scientific/technical merit of the proposed research, including adequacy of the approach and methodology, and identification of clear, measurable goals to be achieved during Phase II.	30%
2. The potential of the proposed research for commercialization, as documented in the offeror's Commercialization Plan and evidenced by (a) the offeror's record of successfully commercializing its prior SBIR/STTR or other research projects, (b) commitments of additional investment during Phase II and Phase III from private sector or other non-SBIR funding sources, and (c) any other indicators of commercial potential for the proposed research.	30%
3. The qualifications of the proposed Principal Investigator, supporting staff and consultants.	25%
4. The adequacy and suitability of the facilities and research environment.	15%

C. PROPOSAL DEBRIEFING

Offerors will be notified promptly in writing if their proposals are no longer being considered for award. Offerors may request a debriefing by submitting a written request to the Contracting Officer within three days of receipt of the notification. Untimely requests may be accommodated at the Government's discretion.

D. AWARD DECISIONS

For proposals recommended for award, the awarding component considers the following:

1. Ratings resulting from the scientific/technical evaluation process;
2. Areas of high program relevance;
3. Program balance (i.e., balance among areas of research); and
4. Availability of funds.

The agency is not under any obligation to fund any proposal or make any specific number of contract awards in a given research topic area. The agency may also elect to fund several or none of the proposals received within a given topic area. The SBIR contract projects do not require establishing a competitive range or requesting final proposal revisions before reaching source selection decisions.

VIII. CONSIDERATIONS

A. AWARDS

1. The award instrument will be a contract.
2. A profit or fixed fee may be included in the proposal, as specified in Federal Acquisition Regulation (FAR) Part 15.404-4. The fee will be negotiated as an element of the potential total contract amount over and above allowable costs.
3. Phase I awards will be firm fixed price contracts. Normally, Phase II awards will be cost-plus-fixed-fee contracts.
4. Normally, Phase I contracts may not exceed $100,000. Phase II contracts normally may not exceed $750,000—including direct costs, indirect costs, and negotiated fixed fee.
5. Cost-sharing is permitted for proposals under this solicitation; however, cost sharing is not required nor will it be an evaluation factor in the consideration of your proposal. Cost-sharing is an explicit arrangement under which the contractor bears some of the burden of reasonable, allocable, and allowable contract cost. If cost-sharing is proposed, it should be reflected in your budget summary.

Approximate number of Phase I contract awards:

AWARDING COMPONENTS		NO. OF AWARDS	ESTIMATED TIME OF AWARD
National Institutes of Health (NIH)	National Cancer Institute (NCI)	38-45	Scientific and Technical Merit Review: May 2007 Anticipated Award Date: July 2007
	National Heart, Lung, and Blood Institute (NHLBI)	7-9	Scientific and Technical Merit Review: February 2007 Anticipated Award Date: August 2007
	National Institute on Alcohol Abuse and Alcoholism (NIAAA)	2	Scientific and Technical Merit Review: March 2007 Anticipated Award Date: June 2007
	National Institute of Child Health and Human Development (NICHD)	2	Scientific and Technical Merit Review: April-May 2007 Anticipated Award Date: August 2007
	National Institute on Drug Abuse (NIDA)	10	Scientific and Technical Merit Review: March 2007 Anticipated Award Date: August 2007
	National Institute of Environmental Health Sciences (NIEHS)	10	Scientific and Technical Merit Review: March 2007 Anticipated Award Date: May 2007
	National Institute of Mental Health (NIMH)	5	Scientific and Technical Merit Review: January 2007 Anticipated Award Date: May 2007
Centers for Disease Control and Prevention (CDC)	Immunization Safety Office (ISO)	1-4	Scientific and Technical Merit Review: February 2007 Anticipated Award Date: August 2007
	National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)	4-6	Scientific and Technical Merit Review: February 2007 Anticipated Award Date: August 2007
	National Center for HIV, STD, and TB Prevention (NCHSTP)	4-6	Scientific and Technical Merit Review: February 2007 Anticipated Award Date: August 2007
	National Center on Birth Defects and Developmental Disabilities (NCBDDD)	1-2	Scientific and Technical Merit Review: February 2007 Anticipated Award Date: August 2007

B. MONTHLY PROGRESS REPORT

Contractors will be required to submit a monthly progress report during Phase I along with their invoice. Phase II reports will be required at intervals stipulated in the terms and conditions of award.

C. FINAL REPORT

Original plus 2 copies

A final report is required of all Phase I and Phase II contractors. It should include a detailed description of the project objectives, the activities that were carried out, and the results obtained. An original and two copies of this report must be submitted as directed by the Contracting Officer not later than the expiration date of the Phase I contract.

Each Phase II "Fast-Track" contractor must submit semi-annual progress reports. A final report is required no later than the expiration date of the Phase II contract. *All reports must be submitted as specified in the contract or as directed by the Contracting Officer.*

D. PAYMENT

The Government shall make payments, including invoice and contract financing payments, by electronic funds transfer (EFT). As a condition to any payment, the contractor is required to register in the Central Contractor Registration (CCR) database before the award of a contract. The registration site for the CCR is http://www.ccr.gov.

Payments on Phase I contracts may be made on a monthly advance basis. Invoices/financing requests submitted for costs incurred under Phase II cost reimbursement contracts will be on a monthly basis unless otherwise authorized by the contracting officer.

E. LIMITED RIGHTS INFORMATION AND DATA

Proprietary Information. Information contained in unsuccessful proposals will remain the property of the offeror. The Government, however, may retain copies of all proposals. Public release of information in any proposal will be subject to existing statutory and regulatory requirements.

The Department of Health and Human Services (HHS) recognizes that, in responding to this solicitation, offerors may submit information that they do not want used or disclosed for any purpose other than for evaluation. Such data might include trade secrets, technical data, and business data (such as commercial information, financial information, and cost and pricing data). The use or disclosure of such information may be restricted if offerors identify it and the Freedom of Information Act (FOIA) does not require its release. For information to be protected, offerors must identify in the Notice of Proprietary Information (on the Proposal Cover Sheet) the page(s) on which such information appears. Any other Notice may be unacceptable to the Government and may constitute grounds for removing the proposal from further consideration without assuming any liability for inadvertent disclosure.

Unless disclosure is required by the FOIA, as determined by FOI officials of the HHS, data contained in those portions of a proposal that have been identified as containing restricted information, in accordance with the Notice of Proprietary Information, shall not be used or disclosed except for evaluation purposes.

The HHS may not be able to withhold data that has been requested pursuant to the FOIA, and the HHS FOI officials must make that determination. The Government is not liable for disclosure if the HHS has determined that disclosure is required by the FOIA.

If a contract is awarded to the offeror as a result of, or in connection with, the submission of a proposal, the Government shall have the right to use or disclose the data to the extent provided by law. Proposals not resulting in a contract remain subject to the FOIA.

Rights to Data Developed Under SBIR Funding Agreement. Rights to data, including software developed under the terms of any funding agreement resulting from a contract proposal submitted in response to this solicitation, shall remain with the awardee. However, the Government shall have the limited right to use such data for Government purposes only.

(1) Each agency must refrain from disclosing SBIR technical data to outside the Government (except reviewers) and especially to competitors of the Small Business Concern (SBC), or from using the information to produce future technical procurement specifications that could harm

the SBC that discovered and developed the innovation.

(2) SBIR agencies must protect from disclosure and non-governmental use all SBIR technical data developed from work performed under an SBIR funding agreement for a period of not less than four years from delivery of the last deliverable under that agreement (either Phase I, Phase II, or Federally-funded SBIR Phase III) unless, subject to paragraph (3)of this section, the agency obtains permission to disclose such SBIR technical data from the awardee or SBIR offeror. Agencies are released from obligation to protect SBIR data upon expiration of the protection period except that any such data that is also protected and referenced under a subsequent SBIR award must remain protected through the protection period of that subsequent SBIR award. For example, if a Phase III award is issued within or after the Phase II data rights protection period and the Phase III award refers to and protects data developed and protected under the Phase II award, then that data must continue to be protected through the Phase III protection period. Agencies have discretion to adopt a protection period longer than four years. The Government retains a royalty-free license for Government use of any technical data delivered under an SBIR award, whether patented or not. This section does not apply to program evaluation.

(3) SBIR technical data rights apply to all SBIR awards, including subcontracts to such awards, that fall within the statutory definition of Phase I, II, or III of the SBIR program, as described in Section 4 of the SBIR Policy Directive, dated September 24, 2002. The scope and extent of the SBIR technical data rights applicable to Federally-funded Phase III awards is identical to the SBIR data rights applicable to Phases I and II SBIR awards. The data rights protection period lapses only: (i) Upon expiration of the protection period applicable to the SBIR award, or (ii) by agreement between the awardee and the agency.

Copyrights. The awardee may normally copyright and publish (consistent with appropriate national security considerations, if any) material developed with PHS support. The awarding component receives a royalty-free license for the Federal Government and requires that each publication contain an acknowledgement of agency support and disclaimer statement, as appropriate. An acknowledgement shall be to the effect that: "This publication was made possible by contract number _____ from (DHHS awarding component)" or "The project described was supported by contract number _____ from (DHHS awarding component)."

Patents. Small business concerns normally retain the principal worldwide patent rights to any invention developed with Government support. Under existing regulations, 37 CFR 401, the Government receives a royalty-free license for Federal Government use, reserves the right to require the patent-holder to license others in certain circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it substantially in the United States.

To the extent authorized by 35 U.S.C. 205, the Government will not make public any information disclosing a Government-supported invention for a four year period to allow the awardee a reasonable time to file a patent application, nor will the Government release any information that is part of a patent application.

Information about additional requirements imposed by 37 C.F.R. 401 should be obtained from local counsel or from:

Office of Policy for Extramural Research Administration,
Division of Extramural Inventions and Technology Resources,
National Institutes of Health (NIH)
6705 Rockledge Dr., MSC 7980
Bethesda, MD 20892-7980
(301) 435-0679 (v)
(301) 480-0272 (fax)
jpkim@nih.gov

Inventions must be reported promptly—within two months of the inventor's initial report to the contractor organization—to the Division of Extramural Inventions and Technology Resources, NIH, at the address above. This should be done prior to any publication or presentation of the invention at an open meeting, since failure to report at the appropriate time is a violation of 35 USC 202, and may result in loss of the rights of the small business concern, inventor, and Federal

Government in the invention. All foreign patent rights are immediately lost upon publication or other public disclosure unless a United States patent application is already on file. In addition, statutes preclude obtaining valid United States patent protection after one year from the date of a publication that discloses the invention.

The reporting of inventions can be accomplished by submitting paper documentation, including fax, or electronically through the NIH Edison Invention Reporting System. Use of the Edison system satisfies all mandated invention reporting requirements and access to the system is through a secure interactive Web site (https://s-edison.info.nih.gov/iEdison) to ensure that all information submitted is protected. In addition to fulfilling reporting requirements, Edison notifies the user of future time sensitive deadlines with enough lead-time to avoid the possibility of loss of patent rights due to administrative oversight. Edison can accommodate the invention reporting need of all organizations. For additional information about this invention reporting and tracking system, visit the Edison home page cited above or contact Edison via email at Edison@od.nih.gov.

Sharing Biomedical Research Resources. It is the policy of the NIH that unique research resources developed with NIH funding must be shared with the research community. Restricted availability of these resources can impede the advancement of research. Principles and Guidelines for Recipients of NIH Research Grants and Contracts, as published in the Federal Register Notice on December 23, 1999 (http://ott.od.nih.gov/NewPages/64FR72090.pdf), provide assistance to determine reasonable terms and conditions for acquiring and disseminating research tools, consistent with the objectives of furthering biomedical research and adhering to the Bayh-Dole Act.

(1) Sharing Research Data. See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html. Offerors shall include in the proposal a plan for data sharing or state why data sharing is not possible.

Reviewers will not factor the proposed data-sharing plan into the determination of scientific merit or score. Program staff will be responsible for overseeing the data sharing policy and for assessing the appropriateness and adequacy of the proposed data-sharing plan.

NIH recognizes that data sharing may be complicated or limited, in some cases, by institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the Privacy Rule. As NIH stated in the March 1, 2002 draft data sharing statement (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-035.html), the rights and privacy of people who participate in NIH-sponsored research must be protected at all times. Thus, data intended for broader use should be free of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual subjects. When data sharing is limited, offerors should explain such limitations in their data sharing plans.

For more information on data sharing, please see our website at http://grants.nih.gov/grants/policy/data_sharing/.

(2) Sharing Model Organisms. All proposals where the development of model organisms is anticipated are to include a description of a specific plan for sharing and distributing unique model organism research resources or state appropriate reasons why such sharing is restricted or not possible. Unlike the NIH Data Sharing Policy, the submission of a model organism sharing plan is not subject to a cost threshold of $500,000 or more in direct costs in any one year. The adequacy of plans for sharing model organisms will be considered by the reviewers when a competing proposal is evaluated. Reviewers will be asked to describe their assessment of the sharing plan in an administrative note and will not include their assessment in the overall score. For additional information on this policy, see the NIH Model Organism for Biomedical Research Website at: http://www.nih.gov/science/models/ and NIH GUIDE Notice OD-04-042: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html.

Royalties. If royalties exceed $1,500, you must provide the following information on a separate page for each separate royalty or license fee:

1. Name and address of licensor.
2. Date of license agreement.
3. Patent numbers.
4. Patent application serial numbers, or other basis on which the royalty is payable.

5. Brief description (including any part or model number of each contract item or component on which the royalty is payable).
6. Percentage or dollar rate of royalty per unit.
7. Unit price of contract item.
8. Number of units.
9. Total dollar amount of royalties.
10. If specifically requested by the Contracting Officer, a copy of the current license agreement and identification of applicable claims of specific patents (see FAR 27.204 and 31.205-37).

F. PERFORMANCE OF RESEARCH AND ANALYTICAL WORK

In Phase I projects, normally a minimum of two-thirds or 67% of the research or analytical effort must be performed by the small business concern.

In Phase II projects, normally a minimum of one-half or 50% of the research or analytical effort must be performed by the small business concern.

The Contracting Officer must approve deviations from these requirements in writing.

Contractor Commitments. Upon entering into a contract, the contractor agrees, in accordance with the terms and conditions of the contract, to accept certain legal commitments embodied in the clauses of Phase I and Phase II contracts. The following list illustrates the types of clauses to which a contractor is bound. This list is not exhaustive. Copies of complete terms and conditions are available upon request.

Clauses That Apply to Contracts *NOT* Exceeding $100,000

1. ***Standards of Work.*** Work performed under the contract must conform to high professional standards.
2. ***Inspection.*** Work performed under the contract is subject to Government inspection and evaluation at all times.
3. ***Termination for Convenience.*** The Government may terminate the contract at any time for convenience if it deems termination to be in its best interest, in which case the contractor will be compensated for work performed and for reasonable termination costs.
4. ***Disputes.*** Any dispute concerning the contract that cannot be resolved by agreement shall be decided by the contracting officer with right of appeal.
5. ***Equal Opportunity.*** The contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin.
6. ***Affirmative Action for Veterans.*** The contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran or veteran of the Vietnam era.
7. ***Affirmative Action for Handicapped.*** The contractor will not discriminate against any employee or applicant for employment because he or she is physically or mentally handicapped.
8. ***Gratuities.*** The Government may terminate the contract if any gratuities have been offered to any representative of the Government to secure the contract.
9. ***American-made Equipment and Products.*** When purchasing equipment or products under an SBIR contract award, the contractor shall purchase only American-made items whenever possible.

Clauses That Apply to Contracts Exceeding $100,000

In addition to the foregoing clauses, the following clauses apply to contracts expected to exceed $100,000.

10. ***Examination of Records.*** The Comptroller General (or a duly authorized representative) shall have the right to examine any directly pertinent records of the contractor involving transactions related to this contract.
11. ***Default.*** The Government may terminate the contract for default if the contractor fails to perform the work described in the contract and such failure is not the result of excusable delays.
12. ***Contract Work Hours.*** The contractor may not require an employee to work more than eight hours a day or forty hours a week unless the employee is compensated accordingly (i.e., overtime pay).
13. ***Covenant Against Contingent Fees.*** No person or agency has been employed to solicit

or secure the contract upon an understanding for compensation except bona fide employees or commercial agencies maintained by the contractor for the purpose of securing business.

14. ***Patent Infringement.*** The contractor shall report each notice or claim of patent infringement based on the performance of the contract.

G. ADDITIONAL INFORMATION

1. This solicitation is intended for informational purposes and reflects current planning. If there is any inconsistency between the information contained herein and the terms of any resulting SBIR contract, the terms of the contract are controlling.
2. Prior to award of an SBIR contract, the Government may request the offeror to submit certain organizational, management, personnel and financial information to assure responsibility of the offeror to receive an award.
3. The Government is not responsible for any expenditures of the offeror in advance and in anticipation of an award. In a cost reimbursement contract, reimbursement of costs by the Government may be made only on the basis of costs incurred by the contractor after award and during performance.
4. This solicitation is not an offer by the Government and does not obligate the Government to make any specific number of awards. Awards under this program are contingent upon the scientific/technical merit of proposals and the availability of funds.
5. The SBIR contract program is not intended as a mechanism to invite unsolicited proposals. Unsolicited SBIR contract proposals shall not be accepted under the SBIR program in either Phase I or Phase II.
6. If an award is made pursuant to a proposal submitted in response to this SBIR solicitation, the contractor will be required to certify that he or she has not previously been, nor is currently being, paid for essentially equivalent work by any agency of the Federal Government.
7. Prior to award of a contract, the contractor will be required to provide a Data Universal Numbering System (DUNS) number. A DUNS number may be obtained immediately, at no charge, by calling Dun and Bradstreet at 1-866-705-5711 or via the Internet at https://eupdate.dnb.com/requestoptions/government/ccrreg/. The contractor must also be registered in the Central Contractor Registry (CCR) prior to award of a contract. Registration can be made via the Internet at http://www.ccr.gov.

IX. INSTRUCTIONS FOR PROPOSAL SUBMISSION

A. RECEIPT DATE

The deadline for receipt of all contract proposals submitted in response to this solicitation is:
5:00 p.m., Eastern Standard Time
Monday, November 6, 2006

Any proposal, modification or revision received at the offices designated below after the exact time specified for receipt is “late” and will not be considered unless it is received before award is made, and

1. There is acceptable evidence to establish that it was received at the Government installation designated for receipt of offers and was under the Government’s control prior to the time set for receipt of offers; or
2. It is the only proposal received.

Acceptable evidence to establish the time of receipt at the Government installation includes the time/date stamp of that installation on the proposal wrapper, other documentary evidence of receipt maintained by the installation, or oral testimony or statements of Government personnel.

If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be received at the office designated for receipt of proposals by the exact time specified in the solicitation, and urgent Government requirements preclude amendment of the solicitation, the time specified for receipt of proposals will be deemed to be extended to the same time of day specified in the solicitation on the first work day on which normal Government processes resume.

Proposals may be withdrawn by written notice received at any time before award. Notwithstanding above, a proposal received after the date and time specified for receipt may be considered if it offers significant cost or technical advantages to the

Government and it was received before proposals were distributed for evaluation, or within 5 calendar days after the exact time specified for receipt, whichever is earlier.

Note: Modifications or revisions to proposals that result in the proposal exceeding the stated page limitations will not be considered.

B. NUMBER OF COPIES

For Phase I, submit the original and 5 copies of each proposal. The Principal Investigator and a corporate official authorized to bind the offeror must sign the original. The 5 copies of the proposal may be photocopies of the original.

For Phase II, see instructions under paragraph VI.

C. BINDING AND PACKAGING OF PROPOSAL

Send all copies of a proposal in the same package. Do not use special bindings or covers. Staple the pages in the upper left corner of each proposal.

X. CONTRACTING OFFICERS AND ADDRESSES FOR MAILING OR DELIVERY OF PROPOSALS

Any small business concern that intends to submit an SBIR contract proposal under this solicitation should provide the appropriate contracting officer(s) with early, written notice of its intent, giving its name, address, telephone, and topic number(s). If a topic is modified or canceled before this solicitation closes, only those companies that have expressed such intent will be notified.

A. NATIONAL INSTITUTES OF HEALTH (NIH)

National Cancer Institute (NCI)

Ms. Mary Landi-O'Leary
Phone: (301) 435-3807
Fax: (301) 480-0309
Email: ml186r@nih.gov

Proposals to the NCI, if mailed through the U.S. Postal Service, must be addressed as follows:

Ms. Mary Landi-O'Leary
Contracting Officer
Office of Acquisitions
National Cancer Institute
6120 Executive Blvd., EPS Room 6044
Bethesda, MD 20892-7222 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NCI*.*

National Heart, Lung, and Blood Institute (NHLBI)

Mr. John Taylor
Phone: (301) 435-0327
Fax: (301) 480-3338
E-mail: taylorjc@nhlbi.nih.gov

Proposals to the NHLBI, if mailed through the U.S. Postal Service, must be addressed as follows:

Review Branch
Division of Extramural Affairs
National Heart, Lung, and Blood Institute
6701 Rockledge Drive
Room 7091
Bethesda, MD 20892-7924 *

**Change the zip code to 20817 if hand-delivered or delivered by an express or other courier service to the NHLBI.*

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Mr. Patrick Sullivan
Phone: (301) 594-7728
Fax: (301) 443-3891
Email: sullivanp@mail.nih.gov

Proposals to the NIAAA must be mailed or delivered to:

Mr. Patrick Sullivan
Contracting Officer
Contracts Management Branch
National Institute on Alcohol Abuse and Alcoholism
5635 Fishers Lane, Room 3016
Bethesda, MD 20892-9304 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIAAA.*

National Institute of Child Health and Human Development (NICHD)

Mr. Robert Stallings
Phone: 301-496-6965
Fax: 301-402-3676
Email: stallinb@mail.nih.gov
Web Site: http://www.nichd.nih.gov/oam_cmb

Proposals to the NICHD must be mailed or delivered to:

Mr. Robert Stallings
NICHD R&D Contracts Management Branch
NIDDK Consolidated Operations Acquisition Center
6100 Executive Blvd., Rm 7A07, MSC 7510
Bethesda, Maryland 20892-7510 *

Overnight/Hand Carry: Rockville, Maryland 20852

National Institute on Drug Abuse (NIDA)

Mr. Craig Sager
Phone: (301) 443-6677
Fax: (301) 443-7595
Email: cs591t@nih.gov

Proposals to the NIDA must be mailed or delivered to:

Mr. Craig Sager
Contracting Officer
NIDA R&D Contracts Management Branch
Neurosciences Office of Acquisition
6101 Executive Boulevard
Room 260, MSC 8402
Bethesda, Maryland 20892-8402 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIDA*.

National Institute of Environmental Health Sciences (NIEHS)

Ms. Jo Ann Lewis
Phone: (919) 541-7894
Fax: (919) 541-2712
Email: Lewis9@niehs.nih.gov

Proposals to the NIEHS must be mailed or delivered to:

Ms. Jo Ann Lewis
Contracting Officer
Office of Acquisitions, OM
National Institute of Environmental Health Sciences
P. O. Box 12874
Research Triangle Park, NC 27709

Proposals to the NIEHS, *if hand-delivered or delivered by an overnight service*, must be addressed as follows:

Ms. Jo Ann Lewis
Contracting Officer
Office of Acquisitions, OM
National Institute of Environmental Health Sciences
79 T.W. Alexander Drive, Building 4401
Research Commons
Research Triangle Park, NC 27709

National Institute of Mental Health (NIMH)

Ms. Suzanne Stinson
Phone: (301) 443-2696
Fax: (301) 443-0501
Email: sstinson@mail.nih.gov

Proposals mailed to the NIMH must be addressed to:

Ms. Suzanne Stinson
Contracting Officer
Chief, Contracts Management Branch
National Institute of Mental Health
6001 Executive Boulevard
Room 8154, MSC 9661
Bethesda, Maryland 20892-9661*

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIMH*.

B. CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

For general administrative SBIR program questions, contact:

Mr. Curt Bryant
Phone: (770) 488-2806
Fax: (770) 488-2828
Email: cbryant1@cdc.gov

National Center for HIV, STD, and TB Prevention (NCHSTP)

Ms. Raquel Powell
Phone: (404) 639-6401
Email: RPowell2@cdc.gov

Proposals to the NCHSTP must be mailed or delivered to:

Ms. Raquel Powell
Team Leader/Contracting Officer
Branch 1/Contracts
CDC/PGO
Corporate Square, Bldg # 8
Mailstop E-15
Atlanta, GA 30329

National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)

National Center on Birth Defects and Developmental Disabilities (NCBDDD)

Mr. Carlos M. Smiley
Phone: (770) 488-2754
Fax: (770) 488-2777
Email: CSmiley1@cdc.gov

Proposals to the NCCDPHP and NCBDDD must be mailed or delivered to:

Mr. Carlos M. Smiley
Contracting Officer
Grants Management Officer
2920 Brandywine Road
Atlanta, GA 30041

Immunization Safety Office (ISO)

Mr. Jeff Miller
Phone: (770) 488-2651
Fax: (770) 488-2777
Email: afx2@cdc.gov

Proposals to the ISO must be mailed or delivered to:

Mr. Jeff Miller
Contract & Grants Management Specialist
Centers for Disease Control and Prevention (CDC)
Acquisition and Assistance,
Branch B, Team IV
2920 Brandywine Road
Atlanta, GA 30341

XI. SCIENTIFIC AND TECHNICAL INFORMATION SOURCES

Health science research literature is available at academic and health science libraries throughout the United States. Information retrieval services are available at these libraries and Regional Medical Libraries through a network supported by the National Library of Medicine. To find a Regional Medical Library in your area, visit http://nnlm.gov/ or contact the Office of Communication and Public Liaison at publicinfo@nlm.nih.gov, (301) 496-6308.

Other sources that provide technology search and/or document services include the organizations listed below. They should be contacted directly for service and cost information.

National Technical Information Service
1-800-553-6847
http://www.ntis.gov

National Technology Transfer Center
Wheeling Jesuit College
1-800-678-6882
http://www.nttc.edu/

Regional Technology Transfer Centers
1-800-472-6785
http://www.ctc.org/NewFiles/RTTCs.html

XII. RESEARCH TOPICS

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE (NCI)

The NCI is the Federal Government's principal agency established to conduct and support cancer research, training, health information dissemination, and other related programs. As the effector of the National Cancer Program, the NCI supports a comprehensive approach to the problems of cancer through intensive investigation in the cause, diagnosis, prevention, early detection, treatment, rehabilitation from cancer, and the continuing care of cancer patients and families of cancer patients. To speed the translation of research results into widespread applications, the National Cancer Act of 1971 authorized a cancer control program to demonstrate and communicate to both the medical community and the general public the latest advances in cancer prevention and management.

SBIR Phase I and Phase II awards may not exceed the limits for total costs (direct costs, facilities and administrative (F&A)/indirect costs, and fee) listed under each topic area.

Phase II proposals may only be submitted upon the request of the NCI Contracting Officer, if not submitted concurrently with the initial Phase I proposal under the Fast-Track procedure (described in Section V). Unless the Fast-Track option is specifically allowed as stated within the topic areas below, applicants are requested to submit only Phase I proposals in response to this solicitation.

This solicitation invites proposals in the following areas:

229 Development of Molecular Pharmacodynamic Assays for Targeted Therapies

Number of anticipated awards: 8

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $750,000

The NCI requests that qualified small businesses submit proposals to develop pharmacodynamic assays for measuring a number of high-priority molecular targets. (For a list of the targets of interest to NCI, please see: http://sbir.cancer.gov/). The short term goal of this contract is to develop new rigorous, validated assays to measure molecular-level response to treatment in conjunction with preclinical development of new candidate therapeutic agents. These assays should measure modulation of molecular targets upon treatment with investigational anticancer therapeutics and support pharmacodynamic studies in animal models and in human tumor and surrogate tissue samples. Real-time assays that could be used to rapidly assess response to treatment in the clinic in conjunction with a clinical trial are highly desirable. Ideally, these assays should also have a known correspondence to tumor modulation in animal efficacy models for the same target. Standard operating Procedures (SOPs) for these assays must be developed and be provided to the NCI along with all supporting data. (To view a sample SOP, please see: http://sbir.cancer.gov/.)

Small businesses may also submit proposals for the development of assays that measure molecular targets relevant to oncology therapeutics development which have been identified by the small business.

The long term goal of this contract is to provide a mechanism to develop a series of molecular pharmacodynamic assays to allow clinical target validation for a wide array of cancer therapeutics to determine earlier in the drug development process if the intended target is modulated and whether this corresponds to either tumor stasis or regression. In addition to the assay itself, the contract recipient will develop and provide to the NCI SOPs that have been fully qualified or validated with human tumor/tissue samples. In addition, the goal is for companies to extend this work into developing research kits or diagnostic agents to stratify patients for clinical trial selection or to evaluate response to new therapeutic agents.

The goal of the NCI SBIR program is to fund small businesses to develop commercially viable products that advance the research and development needs of the Institute. The NCI Strategic Plan identifies validating molecular targets for cancer prognosis, metastasis, treatment response and cancer progression as a strategic priority (Strategy 4.2). Part of this strategy includes creating a library of validated molecular target assays in order to advance broad development of targeted anti-tumor agents. Grant mechanisms thus far have not been an effective method of developing these assays, as they have little publication value. Market analysis indicates that pharmacodynamic assay development is a valuable first step for eventual commercialization of cancer diagnostics and laboratory assays, in addition to serving the needs of cancer therapeutic development.

Two different tracks will be considered:

Track 1 will focus on the development of pharmacodynamic assays for measuring a number of high priority molecular targets. (For a list of the molecular targets of high priority to NCI, please see http://sbir.cancer.gov/.)

This list of molecular targets is being actively pursued by NCI's researchers; thus assays developed under this topic will be good candidates for beta testing at NCI laboratories and clinics. The NCI will determine and periodically re-prioritize the list of molecular targets to be addressed in subsequent years based on the needs of both intramural and extramural investigators.

For Track 2 small businesses are invited to submit proposals for the development of assays that measure molecular targets relevant to oncology therapeutics development which have been identified by the small business.

All proposals will be reviewed by NCI, and overall priority will be given to proposals to develop pharmacodynamic assays of high priority to NCI.

Both tracks will have the following deliverables.

Phase I Activities and expected deliverables:

1. Develop a research pharmacodynamic assay for the molecular target described.
2. Characterize assay reproducibility, variability and accuracy.
3. Deliver to NCI the SOP of the research pharmacodynamic assay for the molecular target described.

Phase II Activities and expected deliverables:

1. Develop a qualified or validated molecular pharmacodynamic assay for the target described. The assay should be applicable in the clinical setting.
2. Perform studies to characterize the correlation between the resulting assay in tumor *versus* surrogate tissues (*e.g.* blood, serum), if applicable.
3. Perform studies to characterize the correlation between the resulting assay in human *versus* animal tissues.
4. Make available to NCI all SOPs for this assay.

Fast-Track justification:

While not necessary for all offerors, there are specific situations where fast track funding would be appropriate and greatly increase the speed of assay development. For example, if the small business recipient has already developed a platform technology for assay development, or similar assays for other molecular targets, the proof of principle can be demonstrated more rapidly.

1. Tangible and specific Phase I deliverables that show significant progress toward development of the technology will be required. The following Phase I deliverables will be used as milestones for continued Phase II funding:
    a. The SBIR recipient must deliver research assay SOPs within 3-6 months.
    b. Demonstrate acceptable real-time assay performance in animal tumor tissue.
2. Before any Phase II funding is awarded, the contract manager must receive both of the tangible milestones written above and verify that the research conducted and SOPs are complete and accurate. Once verified, the contract manager may approve additional Phase II funding.

230 Synthesis of Stable Isotope-Labeled Steroids as Internal Standards for the Measurement of Endogenous Steroid Hormones in Biologic Samples by Liquid Chromatography – Mass Spectrometry (LC-MS)

Number of anticipated awards: 1-3

(Fast-Track proposals in response to this solicitation are encouraged.)

Budget (total costs): Phase I: $150,000; Phase II: $750,000

Short-term project goals: To develop chemical syntheses for specific steroids labeled with stable isotopes and to demonstrate that the products meet defined criteria for use as internal standards in LC-MS measurement of endogenous steroid hormones.

Long-term project goals: To scale up the chemical syntheses of these stable isotope-labeled steroids and combine them in one or more kits. These stable isotope internal standards will permit academic and clinical laboratories to establish sensitive, accurate LC-MS methods for measuring endogenous steroid hormones in biologic samples and to standardize the measurements across laboratories.

Although endogenous steroid hormones, specifically estrogens, androgens, and progestogens, are believed to play critical roles in the etiology of breast, endometrial, ovarian, prostate, and possibly other cancers, research has been limited for many years by the absence of sensitive, accurate methods for measuring the absolute concentrations of steroid hormones and their metabolites in serum, urine, and tissue. The assays routinely used by epidemiologists and clinicians have relied on radiobinding kits with poor specificity and sensitivity in biologic matrixes. Many hypotheses about specific hormone metabolites, genetically-determined patterns of hormone metabolism, and their contributions to cancer prevention, causation, and treatment could not be evaluated. In a multidisciplinary collaboration between the NCI Division of Cancer Epidemiology and Genetics, the NCI Center for Cancer Research, and SAIC-Frederick, LC-MS methods for measuring endogenous estrogens, androgens, and progestogens in urine, blood, and tissue are being developed. The methods are sensitive, accurate, precise, robust, and sufficiently rapid and inexpensive to permit the measurement of endogenous hormones in the multiple biologic specimens collected in epidemiologic and clinical research.

The collaboration has led to the development of a patent-pending, validated high performance liquid chromatography-electrospray ionization-tandem mass spectrometry method for measuring the absolute quantities of 15 endogenous estrogens and their metabolites in human urine. It requires only 0.5 mL of urine, yet is capable of simultaneously quantifying all urinary estrogens and their metabolites in premenopausal and postmenopausal women and men. Details of the current analytical

method, including the identities of the five isotopically labeled standards already being utilized, can be found in Xu *et al*, *Anal Chem* 2005;77:6646-54. The method is now being applied to serum and plasma, anticipating that it will be able to measure all free and conjugated estrogens.

The National Cancer Institute is seeking a contract(s) with a small business(es) capable of preparing pure samples of steroid hormones and steroid hormone metabolites that are labeled with deuterium, C-13, or O-17. It is expected that these labeled steroids will be commercialized by the small business for use as internal standards in LC–MS measurement techniques. The steroid internal standards will be used to ensure accurate, precise, sensitive measurements from LC-MS machines in different laboratories and to minimize intra- and inter-laboratory variability of results.

With these methods, the scientific community will be able to ask important questions about the roles of endogenous estrogens, androgens, and progestogens in the initiation and progression of specific cancers. This method will also be relevant to cancer prevention and treatment. For example, women at high risk of breast cancer could be identified because of inherited or environmentally-induced estrogen metabolism patterns. In addition, the monitoring the effects of various estrogen binding antagonists and estrogen synthesis inhibitors currently being used in breast cancer treatment could be achieved.

Phase I Activities and expected deliverables:

In Phase I, the small business(es) will demonstrate the feasibility of their process. The small business will demonstrate that they can synthesize at least five stable isotope-labeled steroids of those listed below, provide full mass spectra that demonstrate that each of the steroids meet the criteria below, and provide samples of each steroid so that NCI can confirm structure, purity, and stability. The following compounds are of interest:

- estrone, 2-hydroxyestrone, 4-hydroxyestrone, 16α-hydroxyestrone, 2-methoxyestrone, 3-methoxyestrone, 4-methoxyestrone, 17-β-estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 2-methoxyestradiol, 4-methoxyestradiol, 16-keto-17β-estradiol, estriol, 16-epiestriol, 17-epiestriol, 2-hydroxyestrone-3-methyl ether, estrone-3-sulfate, androstenedione, testosterone, dehydroepiandrosterone sulfate, dehydroepiandrosterone, and progesterone.
- Each must be labeled with deuterium, C-13, or O-17; the label can not be placed in the sulfate moiety.
- A full mass spectrum should accompany each preparation delivered and should confirm that no more than 2% of the total mass in the molecular ion region appears at molecular weights smaller than that of the natural material plus 3.
- In addition, a full mass spectrum should demonstrate that even after dissolution in a pH 9 aqueous medium for 10 minutes at 60^{o} C., no more than 2% of the total mass in the molecular ion region appears at molecular weights smaller than that of the natural material plus 3.
- Additional information regarding these specifications can be found at: http://sbir.cancer.gov/.

Phase II Activities and expected deliverables:

- The synthetic methods developed for Phase I must be scaled up for producing at least 0.1 g of each stable isotope-labeled steroid. The larger quantities must meet the criteria listed in Phase I above. Full mass spectra will be required as documentation.
- One or more kits containing stable isotope-labeled steroids will be designed and produced. The kits should allow for an interchangeable suite of isotope-labeled steroids, per the needs of the scientific community.
- Instructions for use of the standards kit.

231 Quantitative Assay for O^{6}-Carboxymethyl Guanine DNA Adducts

Number of anticipated awards: 1

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $750,000

The goal of this project is for the small business to develop and commercialize a kit for quantitatively

measuring O^6-carboxymethyl guanine adducts in human DNA samples.

Nitrosamines are a class of toxic and carcinogenic agents that can form mutagenic DNA adducts. Humans are exposed to preformed nitrosamines through tobacco smoke and other routes, but a substantial source of exposure is endogenous formation in the gut and/or mouth. One import class of nitrosamines is the *N*-methyl-*N*-nitroso compounds that can be metabolized to DNA-reactive intermediates. Epidemiologic studies of the association between nitrosamine exposure and cancer have been hampered by the lack of good exposure metrics for nitrosamines. Recently, the O^6-carboxymethyl guanine DNA adduct has been identified as a potentially useful marker of *N*-methyl-*N*-nitrosocompound exposure because humans seem to lack an efficient repair mechanism for this adduct. Therefore, a very sensitive, high-throughput assay for O^6-carboxymethyl guanine would facilitate epidemiologic studies of nitrosamine exposure and cancer risk.

To date, a single group has reported the development of a polyclonal antibody and associated immunoassay for O^6-carboxymethyl guanine[1-3]. But, the assay has not been successfully applied to the type and number of samples required for epidemiologic studies[4]. Several aspects of the assay could be optimized. First, the assay is based on a single generation of a polyclonal antibody and therefore a novel polyclonal antibody or selection of a best monoclonal antibody may improve assay sensitivity. Alternatively, a non-traditional specific labeling agent, such as an aptamer, may improve sensitivity. Second, although the immuno-slot blot technique previously used might be most sensitive under some conditions, alternative assays should be investigated, such as chemiluminescence enhanced immunoassays, with attention to optimization of plates, blocking agents, titers, and signal boosting system to improve detection and quantitation.

Phase I Activities and expected deliverables: The successful respondent shall devise, create, and test a novel O^6-carboxymethyl guanine identifying system such as, but not limited to, a polyclonal antibody, monoclonal antibody, or aptamer for use on human DNA samples. Other completely novel systems not based on antibodies or aptamers may also be proposed as long as they fulfill the assay requirements. The accuracy, precision, and sensitivity of the novel method shall be tested by (1) measurement of standards with known concentrations of O^6-carboxymethyl guanine such as *in vitro* modified DNA; (2) measurement of standards mixed with extracted human DNA collected from subjects using standard field study methods; (3) the specificity of the reagent should be demonstrated by examining the cross-reactivity with any carriers or links used in reagent production, normal DNA bases, and similar adducts. These demonstrations should show that the novel method has limits of detection and quantitation which exceed current methods. Furthermore, the respondent should demonstrate that the novel method can be assembled as a relatively low cost kit which can be used by a laboratory with the equipment and experience necessary for a typical ELISA or other routine assays (e.g. slot blots). The respondent will supply all required equipment and reagents. The National Cancer Institute will supply limited assistance to the respondent in obtaining normal human DNA for assay development if requested.

Phase II Activities and expected deliverables: The respondent will produce kits for large-scale testing for O^6-carboxymethyl guanine concentrations in human DNA samples from epidemiologic studies, instructions for use of the kits, and instructions for interpretation of the data. The kits shall demonstrate reliable performance characteristics when stored under conditions and for time intervals similar to those required for comparable reagents.

232 Development of Anti-Cancer Agents

Number of anticipated awards: 7

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,500,000

The short term goal of this SBIR contract topic is to create a mechanism whereby candidate therapeutic agents of interest to NCI can be further developed by small businesses. (For a list of the compounds of interest to NCI, please see: http://sbir.cancer.gov/.) (If required, commercialization licenses must be separately negotiated with NIH's Office of Technology Transfer (OTT) and could take the form of a Commercial Evaluation License, a Non-Exclusive License or an Exclusive License to perform pre-clinical development.) Work scope may include animal efficacy testing, SAR, medicinal chemistry, formulation, production of GMP bulk drug and clinical product, pharmacokinetic, pharmacodynamic, and toxicological studies. These data will establish the rationale for continued development of the experimental therapeutic agent

to the point of filing an IND. Ownership of all intellectual property generated in these experiments will be determined by patent law although it is anticipated that experimental data generated by the small business will be owned by the small business, and it may use this information to continue developing the agent independently, or partner with academia or industry in bringing this agent to the clinic (if required, Non-exclusive or Exclusive Licenses must be separately negotiated with the OTT). Successful projects will also be eligible for further development at NCI, including early-stage clinical trials *via* the Joint DCTD-CCR Early Therapeutic Development Program. Non-confidential summaries of compounds available for development will be available on the following web site. Potential applicants will submit a letter of intent and sign a confidentiality agreement in order to receive confidential data on these compounds. For more information, please go to (http://sbir.cancer.gov/).

Companies may also submit proposals for the development of their own agents that are in mid to late pre-clinical development. The development plan, targeted to oncologic indications, will be reviewed by NCI. Overall priority will be given to proposals to develop NCI compounds.

The goal of the NCI SBIR program is to fund small businesses to develop commercially viable products that advance the research and development needs of the Institute. The NCI Strategic Plan identifies integrating clinical trial structures to expedite identification of the most promising treatment opportunities and rapid execution of the necessary clinical trials as a strategic priority (Strategy 4.5). Part of this strategy includes creating an integrated infrastructure to accelerate the implementation of high-priority clinical trials. The long term goal of this contract is to enable a small business to bring a fully developed cancer therapeutic agent to the clinic and eventually to the market.

The NCI's new joint DCTD-CCR initiative for oncology therapeutics development (The Joint DCTD-CCR Early Therapeutic Development Program) seeks to address this strategic objective by reviewing a broad range of candidate therapeutic agents of interest to NCI's basic and clinical investigators, with the goal of capitalizing on FDA's Exploratory IND Guidance to initiate clinical testing at the earliest feasible point in a compound's development.

TRACK I would focus on the development of compounds identified by NCI. The agents being made available by NCI under this solicitation will be in mid to late preclinical development stages (expected time to clinic 1-3 years). NCI has an expressed interest in further development of these agents. Awardees will benefit in several ways:

1. Recommended IND-directed development plan will be prepared by NCI. The contractor is free to propose any procedures or innovative approaches that can shorten the drug development timeline.
2. NCI IP available for licensing – small businesses will be able to capitalize on the investment that NCI has already put into these compounds.
3. Potential for an early-stage clinical development partnership with NCI upon project completion.

Phase I Activities and expected deliverables:

1. Specific activities will range from SAR and medicinal chemistry to animal toxicology and pharmacology, depending on the agent selected for development. The available agents are listed at: (http://sbir.cancer.gov/).
2. Mutually agreed-upon development plan that describes in detail the experiments necessary to file an IND or an exploratory IND.
3. Demonstrate ability to deliver results for the initial set of experiments (project-specific, according to the development plan above).

Phase II Activities and expected deliverables:

1. Complete all experiments according to the development plan (can be re-evaluated if needed).
2. If warranted, provide sufficient data to NCI to file an IND or an exploratory IND for the candidate therapeutic agent in question (oncologic indications).
3. Demonstrate the ability to produce a sufficient amount of clinical grade materials suitable for an early clinical trial (according to FDA's Exploratory IND guidance). http://www.fda.gov/cder/guidance/7086fnl.htm
4. A comprehensive IP and development plan, outlining how the small business will develop and commercialize the subject therapeutic agent. If relevant, finalize clinical co-development agreement with NCI.

TRACK II would allow the development of compounds identified from within the company. The agents should be in mid- to late-stage preclinical development (expected time to clinic 1-3 years). Overall priority will be given to proposals to develop NCI compounds. However, TRACK II awardees will also benefit in several ways:

1. If appropriate, NCI will provide assistance to the small business in its development of an IND-directed development plan. Assistance might include assistance in study design and identification of necessary studies that would be appropriate for filing of an IND;
2. Potential for further collaboration with NCI inventors/investigators;
3. Potential for an early-stage clinical development partnership with NCI upon project completion.

Phase I Activities and expected deliverables:

1. Specific activities will range from SAR and medicinal chemistry to animal toxicology and pharmacology, depending on the agent selected for development.
2. Mutually agreed-upon development plan that describes in detail the experiments necessary to file an IND or an exploratory IND.
3. Demonstrate ability to deliver results for the initial set of experiments (project-specific, according to the development plan above).

Phase II Activities and expected deliverables:

1. Complete all experiments according to the development plan (can be re-evaluated if needed).
2. If warranted, provide sufficient data to file an IND or an exploratory IND for the candidate therapeutic agent in question (oncologic indications).
3. Demonstrate the ability to produce a sufficient amount of clinical grade materials suitable for an early clinical trial (according to FDA's Exploratory IND guidance). http://www.fda.gov/cder/guidance/7086fnl.htm
4. A comprehensive IP and development plan, outlining how the small business will develop and commercialize the subject therapeutic agent. If relevant, finalize clinical co-development agreement with NCI.

233 Development of Software Systems to Facilitate the Use of Electronic Data Records in the Collection of Population-Based Cancer Surveillance Data

Number of anticipated awards: 1-2

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $750,000

The goal of this project is to expand on the present utilization of electronic pathology records in the collection of population-based cancer surveillance data to include electronic records from the other data sources necessary to support overall data collection requirements.

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the United States. The SEER Program currently collects and publishes cancer incidence and survival data from 15 population-based cancer registries and three supplemental registries covering approximately 26 percent of the U.S. population. The SEER database contains information on more than 6 million in situ and invasive cancer cases with approximately 360,000 new cases accessioned each year. The SEER registries routinely collect data on patient demographics, primary tumor site, morphology, histology, extent of disease, stage at diagnosis, first course of treatment, and follow-up for vital status.

About 95% of cancers are first identified through pathology reports, from either hospital based or independent laboratories. A complete cancer record for any given cancer in the SEER database consists of 1) pathology reports that provide key characteristics of the cancer required for its classification, 2) hospital medical records, and 3) other numerous reports (surgical, imagining, treatment) from multiple institutions. Historically, this data gathering has been performed manually, either by cancer registrars from the central registry, who travel to the various data sources and abstract reports, or by relying on hospital-based cancer registrars who forward their reports to a central registry. These methods are labor-intensive, time-consuming, and may result in data of varying quality and completeness.

Although many data sources are available in electronic format, to date, with the exception of an ongoing effort to utilize electronic pathology reports

(E-Path) in case finding, no other electronic data are captured for cancer registries. No mechanism exists for searching electronic health records at their source, selecting those which relate to a reportable cancer, applying the appropriate codes to the relevant data fields and transmitting both the appropriate records and coded data to the responsible central cancer registry. Utilization of electronic records in the reporting of cancer surveillance data has the potential to improve data quality and completeness by removing the laborious, time-consuming manual data collection effort currently in place (1-7).

The key to improving the cancer surveillance system in the U.S. is the timely collection and integration of patient information from multiple sources within a medical care environment and across multiple institutions. An electronic central cancer registry opens the possibilities of adding additional information such as results of emergent biomarker tests and treatment information.

Processing the new electronic records would be similar to how the electronic pathology reports are processed. Modifications would involve changes to both the report generation and extraction, data translation, report selection and transmission, and coding system, which would require unique solutions dependent on the source of the case data (for example, medical record, diagnostic imagining, etc.).

Phase I Activities and expected deliverables:

- From the various available record sources (e.g., medical records, billing claims records, surgical reports, treatment reports, etc.), determine which are available electronically to large hospital or independent cancer treatment centers.
- From what is available electronically, evaluate which source(s) would be most beneficial to central registry reporting. Examples of benefits include, but are not limited to 1) capturing limited data in a much more timely fashion, 2) capturing a category of data more reliably and completely, or 3) other ways of enhancing cancer registration in a cost and time effective way for personnel.
- Determine which software products currently provide for processing of text-based medical data from one or more sources within a hospital which may serve as a platform for expansion into the selected record source(s). For example, a system which performs a natural language parsing of medical claims data to select cases where patients have been discharged following bypass surgery, may be modifiable to select for cancer discharges.
- Convene focus groups or conduct interviews with potential end-users of the system to determine if the system contents, format, etc. are appropriate for ease of use.
- Develop a working prototype of the system.
- Include travel funds to present Phase I findings and demonstrate product prototype to an NCI Evaluation Panel.

Phase II Activities and expected deliverables:

- For the selected record source, develop the standards for the transmission of the electronic health records (entailing both an HL7 and a text file standard) from their source to the central cancer registry. These standards currently do not exist for any potential source. An effort is currently underway to establish standards for the transmission of reportable pathology reports from the laboratory to the cancer registry (8).
- For the selected record source, develop the rules needed to select the potentially reportable records from the data source. The rules necessary for the selection of potentially reportable pathology reports will not be the same as those for various other source reports. Each report source (such as the diagnostic imaging report, hospital medical record, surgical report, etc.) requires a different set of rules and requirements which must be identified and tested. The electronic pathology systems have the ability to transform English text into machine readable codes corresponding to required standardized medical nomenclatures, however, these systems only relate to the information found within a pathology report and must be expanded as additional source records are to be processed.

- For the selected record source, development of a demonstration system which can receive the transmitted source records, parse the report text, and utilizing the rules developed for the selection of reportable cancer cases, select the appropriate records.
- Describe Universal Modeling Language (UML) models of all architecture components.
- Develop the final software product that implements the market-validated features, functions and requirements developed in Phase I.
- Demonstrate the sensitivity and specificity of reportable case selection in the range currently demonstrated in electronic pathology systems - 98-99% range for both sensitivity and specificity. Evaluate the use of the final software with potential end-users.
- Provide the technical documentation of the system, including UML models, system architecture, programming interfaces, and supporting software requirements.
- Identify Phase II barriers to evaluating the impact of the software and resolutions to these barriers.
- In the first six months of the first year of the contract, provide the program and contract officers with a letter of commercial interest.
- In the first six months of the second year of the contract, provide the program and contract officers with a letter of commercial commitment based on the successful outcome of the Phase II.
- Include $24,000 in the budget for an independent vendor to evaluate the final product.
- Include sufficient travel funds for the P.I. to participate in an NCI/DCCPS SBIR Showcase.
- Prepare at least one manuscript describing the development and evaluation of the product for publication in a peer-reviewed scientific journal.
- Submit final report in the template provided by the NCI program officer.

234 Develop Automated Methods to Identify Environmental Exposure Patterns in Satellite Imagery Data

Number of anticipated awards: 1-2

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $750,000

The NCI seeks to develop an automated process to apply existing pattern recognition algorithms to satellite image data and present the results to the researcher that employs a user-friendly, interactive geovisualization tool. Useful features of the automated process include options to use smoothing techniques, cluster identification, change detection, isopleth map production and animation to clearly illustrate the pattern-identified images of health-(preferably cancer-) related environmental measures over time. It would also be important to include, if possible, any existing algorithms to convert raw image values to categorized factors, such as crop maps, soil content or water quality to permit the geovisualization tool to operate on these derived, as well as original, values.

A requirement of the process will be that it can manage, process, and distribute satellite images, and orthorectify (geographically register) the piecewise images from multiple satellite passes over a geographic area and present a unified image of the entire area. This is an important first step to be able to use satellite imagery for environmental exposure assessment on a routine basis.

Location-specific data have become increasingly important for cancer research. Cancer mortality, morbidity, and survival rates are known to vary by place. A growing body of research has shown the importance of local neighborhood influences on cancer outcomes, risk behaviors, and access to care (Kirby and Kaneda 2005; Cubbin 2000). Researchers in cancer surveillance, cancer control, health disparities, and other areas now routinely collect information on location of patient residence and potential risk factor exposures from a variety of sources.

GIS software capabilities and statistical methods for analyzing geospatial data have advanced rapidly over the past decade. When NCI first published an atlas of cancer mortality in 1975, only the National

Oceanic and Atmospheric Administration had software locally available to produce the maps. Now, maps can be produced on a desktop PC or handheld PDA using available software. The volume of data used for location identification has increased rapidly, due to technological advances through a Global Positioning System (GPS) that has input data from the ground or from satellite imagery. These high volume data streams or images must be processed quickly and have the ability to integrate into existing geospatial databases.

Satellite imagery has been used to estimate an individual's probable exposure to agricultural pesticides (Ward 2000; Nuckols 2004) and water quality (Xiao 2006). LandSat satellite images are now available for many areas from the past 30 years, making them a potentially useful source for identification of historic environmental exposures for cancer studies. While methods exist for detecting patterns and converting image data to potential exposure estimates, the volume of satellite data has outgrown the application potential for these methods to effectively estimate exposures. The integration of millions of available time-specific images is prohibitive.

Currently, it is not possible to integrate images or data streams from numerous data sources to attempt smoothing techniques, cluster identification, isopleth map production and animation to analyze the pattern-identified images over time when multiple years of cancer and potential exposure data are under consideration. Therefore, inferences between cancer outcomes and potential exposures may not be realized.

Cancer research and health research have not grown technologically at the same pace. Frequently cancer and health researchers are unable to take advantage of the technological advances seen in other scientific fields due to database and methodological limitations.

Phase I Activities and expected deliverables:

- Review the literature to determine types of environmental exposures that have both been associated with increased cancer risk and can be measured from satellite data. Determine what, if any, algorithms exist to convert raw satellite image values to exposure measures.
- Determine what, if any, commercial software products exist that may serve as a platform for the proposed geovisualization tool. For example, the proposed product might be best developed as an add-on to an existing GIS, image analysis or data visualization package.
- Evaluate the availability of satellite images over the U.S. by time for a representative set of desired exposure measures. Identify problems with comparability and availability of data over time and as collected by different satellite monitoring systems.
- Convene a focus group of environmental epidemiologists and other interested scientists to solicit input on the functionality required for the proposed product.
- Develop a statement of functional requirements and user interface requirements for the product.
- Develop a working prototype of the system using a sample of existing satellite imagery data.
- Include funds to present Phase I findings and demonstrate product prototype to NCI staff.

Phase II Activities and expected deliverables:

- Conduct a formal usability study of the software with representative users to evaluate the prototype developed in Phase I. Enhance and modify the prototype's functionality and user interface based on this feedback.
- Demonstrate the accuracy of the derived patterns in the images by comparing results of application of the software to published results or by simulating images that appear similar to that used in published work.
- Demonstrate the flexibility of design that would permit updating the software as new image categorization algorithms or satellite image formats are added.
- Complete the development of the full software package, including technical documentation.

- Identify Phase II barriers to evaluating the impact of the software and resolutions to these barriers.
- In the first six months of the first year of the contract, provide the program and contract officers with a letter of commercial interest.
- In the first six months of the second year of the contract, provide the program and contract officers with a letter of commercial commitment based on the successful outcome of the Phase II.
- Include $24,000 in the budget for an independent vendor to evaluate the final product.
- Include sufficient travel funds for the P.I. to participate in an NCI/DCCPS SBIR Showcase.
- Prepare at least one manuscript describing the development and evaluation of the product for publication in a peer-reviewed scientific journal.
- Submit final report in the template provided by the NCI program officer.

235 Home Centered Coordinated Cancer Care System

Number of anticipated awards: 1-2

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $750,000

The Veterans Health Administration, with its enterprise wide computerized patient record, telehealth technologies and coordinated care model, offers a working prototype of a home based system of coordinated care for chronic conditions. The VHA, in partnership with NCI, has developed a system of coordinated cancer care made up of these components. This system has shown promise for the effective management of symptoms and high quality of life during cancer treatment. It has the additional potential of saving costs due to unnecessary institutionalization. The health information infrastructure that supports this system requires a high level of interoperability as does the human communication processes that make the coordination among the team seamless and dependable. The VA/NCI cancer care coordination processes are similar to disease management processes. They are led by a professional care coordinator who brings community resources to bear upon the various symptoms as they are experienced by the patient. The care coordinator is responsible for monitoring the patients' symptoms on a daily basis and providing feedback regarding appropriate self or professional symptom management actions given the patient's current status. The patient and/or informal caregiver is responsible for answering daily questions and implementing self care symptom management. Daily patient/provider dialogue is supported by a telehealth program that is linked to the VA's computerized health record.

The goal of this project is to develop an automated coordination tracking program that will allow all cancer care team members a view of the VA/NCI cancer care coordination processes. An automated cancer care coordination tracking program will track health status and outcomes data, symptom management recommendations, interventions and decision points in real time and in full view of all team members. It will register handshakes (responsibility hand-offs) and all feedback loops throughout the coordination of a given activity. Ideally this software should include a real time visual simulation of the coordination process with alerts, reminders and other signals that support the accountability of individual team members and the integrity of the entire coordination effort. This program is not to be a stand alone product but should be integrated into a larger system of home based coordinated cancer care.

In early 2003 the NCI announced its goal of "eliminating the suffering and death due to cancer by 2015." There is an expected total of 1,358,030 new cancer cases in the US in 2005 (Jemal, Murray, & Ward, 2005). Among 19 million outpatient visits made by cancer patients each year, chemotherapy is administered in approximately 22% of those visits (Hewitt & Simone, 1999). Cancer chemotherapy successfully treats many cancer cells, but causes severe symptoms, such as fatigue, pain, and nausea (Mooney, Beck, & Friedman, 2002). Uncontrolled symptoms, many of which can be profound and are primarily experienced by patients at home, are associated with a reduction in health-related quality of life (HRQL) (Cooley, Short, & Moriarty, 2003; Mooney et al., 2002). A recent study of 117 lung cancer patients found that many symptoms (e.g., pain and fatigue) decreased from 0 to 3 months, but from 3 to 6 months pain and fatigue increased markedly (Cooley et al., 2003). Patients' quality of

life is too often compromised as a result of either the cancer and/or its treatment (Hammerlid, Silander, & Hornestam, 2001). The current standard of practice for managing symptoms during chemotherapy is for a health provider to address them when the patient comes in to the hospital or clinic for treatments, sometimes days or weeks apart (NIH, 2002).

In an effort to reduce suffering due to cancer and its treatment's side effects in a more effective manner, the Health Communication and Informatics Research Branch in the Division of Cancer Control and Population Studies at NCI has partnered with the Veterans Health Administration (VHA) to develop and test a model of coordinated cancer care. We have designed, implemented, and tested a working model based upon a systems view of human communication and informatics and upon the VA's Community Care Coordination Service model (Harris, L; Kobb, R; Ryan, P; Darkins, A; Kreps, G. "Research as Dialogue: Health Communication and Behavior Change in Patients' Natural Habitat" in Whitten, P and Cook, D (Eds) *Understanding Health Communication Technologies.* San Francisco, Jossey Bass. Pp91-100; Chumbler, N; Richardson, L; Harris, L, et al. "Cancer Care Dialogues: Empirical Support for Complex Adaptive Systems Research and Practice" in Whitten, P., Kreps, G.L., & Eastin, M. (Eds.). (2006, In press). *Advances in Cancer Online Information Services.* Cresskill, NJ: Hampton Press; Meyer, M; Kobb, R; and Ryan, P. "Virtually Healthy: Chronic Disease Management in the Home" *Disease Management,* Vol 5, No.2, 2002, pp87-94.

The VA/NCI home centered coordinated cancer care system holds promise for the thousands of Veterans who have cancer. We expect this project to standardize and extend this model to others outside the VA.

Phase I Activities and expected deliverables:

- Review the VA/NCI cancer care coordination model, other coordination protocols and relevant literature to develop an overall cancer coordination process model;
- Establish a team or set of teams that will conduct cancer care coordination, including their roles and responsibilities;
- Conduct interviews with team members and selected community participants to develop a set of use case scenarios (from diagnosis through survivorship/death for one cancer type) that will serve as the basis of the coordination simulation software program;
- Provide a report detailing the coordination tracking program design, including a theoretical and methodological bases for the evaluation;
- Provide a set of use case scenarios that have been approved by members of the team for tracking;
- Develop a prototype of the cancer care coordination tracking program;
- Obtain letters of agreements from appropriate community participants to participate in the testing and evaluation of the cancer coordination system in the Phase II;
- Convene focus groups or conduct interviews with potential end-users of the system to determine if the system contents, format, etc. are appropriate for ease of use.
- Develop a working prototype of the system.
- Include travel funds to present Phase I findings and demonstrate product prototype to an NCI Evaluation Panel.

Phase II Activities and expected deliverables:

- Complete 2 iterations of the tracking program software, including technical documentation of the system and a training manual;
- Develop evaluation measures;
- Evaluate and refine the program based upon user feedback;
- Integrate the tracking program into a telehealth monitoring and computerized patient record;
- Test and evaluate the complete system serving cancer patients and their care coordination team using process and outcome measures as described above;
- System Requirements include:

- Embedding the tracking software into a home telehealth monitoring and reporting system based upon the VA/NCI model of home centered coordinated cancer care; this could involve partnering or licensing with other vendors or developers of these components.
- Integrating the home centered coordinated cancer care system into a community's existing IT infrastructure using the IT interoperability standards offered by The U.S. Department of Health and Human Services (www.hhs.gov/healthit). Eligible communities are those that have been funded by The Foundation for eHealth Initiative which provides seed funding and support to multi-stakeholder collaboratives within communities (both geographic and non-geographic) who are using electronic health information exchanges (HIE) and other information technology tools to drive improvements in healthcare quality, safety, and efficiency (www.ehealthinitiative.org).
- Evaluating the system in a real community setting, according to cost, quality of care, quality of life and access outcome measures in addition to the community's own health and IT standards. Community members should be included in the research and development team from the beginning of the research and development project.

- In the first six months of the first year of the contract, provide the program and contract officers with a letter of commercial interest.

- In the first six months of the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment based on the successful outcome of the Phase II.

- Include $24,000 in the budget for an independent vendor to evaluate the final product.

- Include sufficient travel funds for the P.I. to participate in an NCI/DCCPS SBIR Showcase.

- Prepare at least one manuscript describing the development and evaluation of the product for publication in a peer-reviewed scientific journal.

- Submit final report in the template provided by the NCI program officer.

236 Antibody Array for Cancer

Number of anticipated awards: 3

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $800,000

The purpose of this initiative is to develop high throughput antibody arrays for quantitative analysis of multiple biomarkers for early detection and diagnosis of cancer. These arrays may include antibodies based on the applicant's own research and knowledge of the literature. Applicants are also encouraged to contact extramural investigators from the NCI's Early Detection Research Network (EDRN; www.cancer.gov/edrn), which is developing a number of biomarkers for cancer detection, diagnosis and prognosis. Please contact one of the members or associate members at: http://edrn.nci.nih.gov/memberslist/x.xml. The selected applicants will develop microarrays, the chemistry of which may be based on nanotechnology and or microfluidics. Applicants should focus initial development for the diagnosis and early detection of prostate, breast, lung, colon, and other major epithelial cancers. In Phase II, the antibody microarray developed in Phase I will be validated under a plan developed with the NCI project officer. Applicants are encouraged (but not required) to develop a validation plan that includes the participation of EDRN investigators. It is anticipated that such participation will result in accelerated development, production, validation and commercialization of antibody microarray technology for early detection and diagnosis of cancer. The specific objectives are:

- Prepare and purify biomarker-specific antibodies in the form of recombinant antibodies or monoclonal antibodies (mAb) and construct arrays;

- Develop and/or improve methodologies for quantitative measurements of the bound antigens on Ab microarrays;

- Perform analytical validation, e.g., check for reproducibility, sensitivity, specificity and dynamic range of detection in collaboration with EDRN and other institutions to measure the efficacy of the developed array.

Currently, there is no single marker or a combination of biomarkers that has sufficient sensitivity and specificity to diagnose early stage cancer. However, recent developments in gene and proteomic profiling of precancerous and cancerous lesions suggest that a combination or a patterns of markers may be used to distinguish between cancer and non-cancer with high sensitivity and specificity (95-100%). Innovative technologies, such as microfluidics and nanotechnology, combined with antibody arrays are likely to provide a reliable, sensitive and quantitative detection tool for measuring differentially expressed biomarkers from a limited amount of sample (20ul or less of serum). The involvement of small businesses through the SBIR contract mechanism will strengthen the EDRN's efforts in the development, validation and commercialization of biomarkers for early detection and risk assessment.

Intellectual property: The work performed under this contract is between a selected Biotech Company and EDRN Investigator/s and the NCI EDRN Program staff. Unless otherwise agreed to in writing between the selected Biotech Company and the institutions of the EDRN, the following will guide the Intellectual Property management and sharing of research resources generated from the work performed under this contract. All inventions conceived or first actually reduced to practice solely by the selected Biotech Company investigators under this Agreement will be the property of the selected Biotech Company in accordance with 35 USC Section 200, et. seq., subject to any intellectual property (IP) rights of the providers of biomarkers (e.g., institutions of EDRN investigators) to the selected Biotech Company. All inventions conceived or first actually reduced to practice jointly by the selected Biotech Company and any EDRN Investigators or NCI EDRN program staff will be jointly owned by the inventors' institutions. The Selected Biotech Company agrees that it will permit EDRN Investigators to use such inventions under terms consistent with the *Principles for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical research Resources* (http://grants.nih.gov/grants/intell-property_64FR72090.pdf).

The providers of biomarkers will retain their respective IP rights for those biomarkers developed by their institution's respective investigators. The selected Biotech Company is responsible for negotiating access rights, including any commercial license rights, to all materials provided to the selected Biotech Company, and any related IP, in order to conduct the activities funded under this Agreement.

NCI, EDRN Investigators and the EDRN Data Management and Coordinating Center, managed by the Fred Hutchinson Cancer Research Center ("EDRN DMCC") will have unlimited rights as defined in FAR 52.227-14, general to the following data developed during the course of this project: (i) protocols for using the antibody microarrays to be developed by the selected Biotech Company and individual antibodies independent of the antibody arrays; (ii) initial research results concerning the use of antibodies against specimens provided by EDRN Investigators; (iii) antibody characterization data, including the results of testing to demonstrate the utility of particular antibodies; and (iv) validation data based on subsequent experiments involving the antibody microarrays.

Authorship of publications resulting from data developed under this contract will be shared by all contributing parties including the NCI.

Phase I Activities and expected deliverables:

Establish the proof of principle – develop an antibody microarray for detection of 3 biomarkers using innovative technologies, and demonstrate that the tiled antibodies perform as well or better than a conventional ELISA in the detection of these biomarkers in serum from cancer patients. Relevant biomarkers could be selected from published literature or by contacting one the EDRN extramural investigators. (Please contact one of the members or associate members at: (http://edrn.nci.nih.gov/memberslist/x.xml.)

Phase II Activities and expected deliverables:

Develop antibody microarrays with a capability to simultaneously detect and measure the concentration of 30-50 biomarkers. These arrays can include both biomarkers from the EDRN as well as biomarkers identified by the small business; 2) Validate antibody microarrays in high-risk subjects. Applicants are encouraged (but not required) to develop a validation plan that includes the participation of EDRN investigators. Validation stage

may require production and testing of up to 1000 microarrays with samples from normal and case subjects.

237 Glycan Arrays for Biomarker Discovery and Validation

Number of anticipated awards: 3

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $800,000

Despite the fact that numerous examples of tumor-associated glycans, such as T, Tn, sialyl-Tn, Sialyl Lewis X, Sialyl Lewis have been discovered, they likely represent a small proportion of all glycan structures that distinguish normal from neoplastic cells. Studies to systematically identify and exploit cancer-specific glycan biomarkers are urgently needed. Glycans are oligosaccharides, the structures of which may range from a simple linear structure to a more complex, branched structure. The purpose of this contract is to develop technologies to characterize glycan moieties of glycoproteins, such as CA125 to enhance the diagnostic capability of protein-based biomarkers. Development of such technologies may greatly benefit from microchip-based technologies developed for DNA and protein arrays. Through this initiative, the Offerors are expected to utilize existing tools for the development of glycan arrays. These arrays may include glycans based on the applicant's own research and knowledge of the literature. Applicants are also encouraged to contact extramural investigators from the NCI's Alliance of Glycobiologists for Cancer Detection and Diagnosis, which is developing a number of biomarkers for cancer detection, diagnosis and prognosis. (For a list of appropriate extramural investigators, please see: http://sbir.cancer.gov/). Promising glycomic biomarkers developed by this program will be channeled into the EDRN for clinical validation highlighting the translational priority of this effort.

The search for tumor-specific antigens has revealed a plethora of cell surface glycans that could be pursued as molecular markers of cancer. Glycolipids, in particular, expose these tumor-specific epitopes through their oligosaccharide moieties oriented toward the extracellular face. An altered glycolipid profile often correlates with metastatic potential of the tumor. While the literature is rich in examples of glycan-based tumor antigens, it appears little effort has been made to exploit specific glycans as cancer biomarkers. There has, however, been some focus to employing glycan-targeted antibodies as therapeutic agents against cancer. Several clinical trials taking this immunotherapy approach have been undertaken. There is evidence that glycans associated with tumor markers, such as MUC1, MUC2, CA19-9 may confer higher sensitivity and specificity to the already existing biomarkers that have been found clinically useful. It is therefore important to rapidly identify clinically-useful glycans using high throughput technologies.

Intellectual property: The work performed under this contract is between a selected Biotech Company and EDRN Investigator/s and the NCI EDRN Program staff. Unless otherwise agreed to in writing between the selected Biotech Company and the institutions of the EDRN, the following will guide the Intellectual Property management and sharing of research resources generated from the work performed under this contract. All inventions conceived or first actually reduced to practice solely by the selected Biotech Company investigators under this Agreement will be the property of the selected Biotech Company in accordance with 35 USC Section 200, et. seq., subject to any intellectual property (IP) rights of the providers of biomarkers (e.g., institutions of EDRN investigators) to the selected Biotech Company. All inventions conceived or first actually reduced to practice jointly by the selected Biotech Company and any EDRN Investigators or NCI EDRN program staff will be jointly owned by the inventors' institutions. The Selected Biotech Company agrees that it will permit EDRN Investigators to use such inventions under terms consistent with the *Principles for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical research Resources* (http://grants.nih.gov/grants/intell-property_64FR72090.pdf).

The providers of biomarkers will retain their respective IP rights for those biomarkers developed by their institution's respective investigators. The selected Biotech Company is responsible for negotiating access rights, including any commercial license rights, to all materials provided to the selected Biotech Company, and any related IP, in order to conduct the activities funded under this Agreement.

NCI, EDRN Investigators and the EDRN Data Management and Coordinating Center, managed by the Fred Hutchinson Cancer Research Center ("EDRN DMCC") will have unlimited rights as

defined in FAR 52.227-14, general to the following data developed during the course of this project: (i) protocols for using the antibody microarrays to be developed by the selected Biotech Company and individual antibodies independent of the antibody arrays; (ii) initial research results concerning the use of antibodies against specimens provided by EDRN Investigators; (iii) antibody characterization data, including the results of testing to demonstrate the utility of particular antibodies; and (iv) validation data based on subsequent experiments involving the antibody microarrays.

Authorship of publications resulting from data developed under this contract will be shared by all contributing parties including the NCI.

Phase I Activities and expected deliverables:

1. Establish the proof of principle. Develop and validate arrays of a minimum of 50 glycans derived from the known cancer biomarkers in consultation with the NCI Project Officer. These arrays can include both glycans from the EDRN as well as glycans identified by the small business.
2. Test the cancer-specificity of glycan arrays in a variety of serum samples.

Phase II Activities and expected deliverables:

1. Validate the arrays developed in Phase II with sera obtained from normal and cancer patients;
2. Demonstrate the clinical utility of array with human sera;
3. Measure performance characteristics (sensitivity, specificity) of glycan arrays.

238 Development of Clinical Automated Multiplex Affinity Capture Technology for Detecting Low Abundance Cancer-related Proteins/Peptides

Number of anticipated awards: 3

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

Of the hundreds of thousands of proteins believed to be found in different body fluids, it is likely that cancer-related proteins will be in relatively low abundance. The development of effective technologies to accurately measure these proteins and improve our diagnostic capabilities by discerning diseased from non-diseased states requires the development of next-generation proteomic technologies. The purpose of this project is to stimulate the development of quantitative automated affinity/protein capture multiplex technologies for measuring low abundant cancer related proteins/peptides from bodily fluids in support of the Clinical Proteomic Technologies for Cancer initiative. In addition, this tool as conceived is to be applicable in Cancer Centers and other settings where NCI Investigators conduct clinical care.

The application of proteomics tools in the clinical setting lags far behind their use in basic science and drug discovery. In the past, protein/peptide biomarkers were tested individually to determine their value using common techniques such as ELISA, 2-D gels, and mass spectrometry. Each of these technologies has its advantages, but they still suffer from an inability to quantitatively evaluate multiple markers in a single reaction. Multiplexing capability is becoming a critical parameter in clinical biomarker evaluation today, as testing practices employing a single marker do not have the performance characteristics required to enable critical decision making. While some new technologies capable of measuring multiple biomarkers in a single assay has emerged, they typically suffer from low precision (CV's as high as 50%), an inability to detect physiological levels of low abundant proteins, and automation. Despite these shortcomings, the advantage gained by miniaturization, high sensitivity, high-throughput, and automation makes affinity/protein capture technologies a potentially powerful technology for the quantitative detection of known protein markers and the discovery of new markers.

Therefore, the NCI is interested in proposals that focus on developing a quantitative automated high-throughput multiplex affinity/protein capture technology for detecting low abundant cancer related proteins/peptides from bodily fluids (examples of "bodily fluids" include plasma or serum, urine, serous fluids collected from body cavities, saliva, and ductal lavage, but not cell lysates or tissue culture media). Proposals should describe how the proposed technology will be highly specific, highly selective and have ultra-sensitive detection capabilities (at least within the ng/mL range) with limited sample preparation. Proposals should also distinguish any new methods of multiplex fabrication, novel affinity/protein capture systems, and/or new detection/quantification systems. All responses must deliver a reasonable method for working with

complex bodily fluids. In addition, maximum level of multiplexing, volume of sample requirement, with sample processing/analysis time must be addressed.

Phase I Activities and expected deliverables:

- Demonstration of feasibility of the innovative approach.
- Produce and initial product prototype in working with the Clinical Proteomic Technologies for Cancer community.
- Conduct usability testing with product prototype with representative users (e.g. Clinical Proteomic Technologies for Cancer community).
- Make modifications to the prototype based on results obtained from usability testing.
- Compare findings to ELISA-based technologies. Detection limits should aim to be measured and reported as absolute quantitations that equal or surpass current ELISA measurements.
- Prototype requirements include sample volumes less than 50 microliters, multiplex a minimum of 5 markers, high sensitivity (detection limit lower than 5 picogram/microliter), high reproducibility (CV's less than 10%), and broad dynamic range (gram/Liter to nanogram/Liter)
- Establish prototype revisions/additions to be implemented and tested in Phase II.
- Present findings to an NCI Evaluation Panel.
- Research should be proposed with quantitative feasibility milestones.

Phase II Activities and expected deliverables:

- Implement strategy and project plan for a fully functional quantitative, automated high-throughput multiplex affinity/protein capture technology for detecting low abundant cancer related proteins/peptides from bodily fluids.
- Specificity greater than 95%.
- Development of an affinity/protein capture technology with multiplexing capability up to 50 analytes (proteins/peptides) that implements the features, functions, and requirements developed in Phase I. Project to be done in conjunction with the Clinical Proteomic Technologies for Cancer community.
- Validate findings to ELISA.

239 Development of Alternative Affinity Capture Reagents for Cancer Proteomics Research

Number of anticipated awards: 3

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

Today, existing biotechnology reagent companies produce thousands of antibodies per year. Many of these are commercially available. However, many of these antibodies are known to be poorly characterized and suboptimal across multiple applications. Polyclonal antibodies lack the reproducibility of monoclonal antibodies. Likewise, the production of monoclonals is expensive and may take 6-8 months to produce. Even after production, there is no guarantee that a monoclonal antibody will be specific for the target of interest, will work in the needed assay, or can be used in combination with other antibodies due to an antibody's large size and subsequent competition for overlapping binding domains. As such, the high costs associated with producing even small quantities of monoclonal antibodies represent a large barrier towards cost-effective reagents and resources for proteomic technology research and clinical adaptation. The goal of this project is to develop reproducible, highly qualified/characterized alternative protein capture reagents for the cancer research community. The development of these affinity capture reagents will be done in coordination with NCI's Clinical Proteomic Technologies for Cancer initiative and be targeted to a list of over 100 purified recombinant proteins being constructed and characterized through this initiative.

The National Cancer Institute has developed intensive programs in the field of clinical proteomics to understand and quantify the alterations that occur in proteins that will play a significant role in the early diagnosis and effective treatment of cancer in the 21st century. In an effort to accelerate the development of clinical protein detection systems,

the NCI held a series of scientific and technical meetings with leading experts (scientists, physicians, clinicians, and engineers) in this field by addressing technology development, standardization, implementation and integration of the most robust proteomic technologies that could be routinely used in a clinical setting. The first of these meetings was held in April 2002 with the most recent in February 2006. These meetings identified and defined effective strategies that the NCI should take to address the many challenges of clinical cancer proteomics. At the Proteomic Technologies Reagents Resource Workshop held on December 2005, there was strong support for the development of renewable, alternative capture reagents that could be produced more efficiently and cost-effectively than monoclonal antibodies and hence, provide an inexpensive, well-characterized resource for the scientific community. Several technologies such as yeast single chain antibodies, “nanobodies,” or synthetically produced capture reagents such as aptamers and nanotechnology reagents demonstrate a potential for alternative, reproducible, cost-effective reagents in proteomics research.

Therefore, the NCI is interested in proposals that focus on developing alternative affinity capture reagents that can effectively compete against ELISA-based antibody technologies in terms of protein recognition, binding affinity, and detection and can be reproducibly produced in a cost-effective and efficient manner. These affinity reagents will ultimately be designed to target proteins developed in coordination with the Clinical Proteomic Technologies Initiative for Cancer that is producing purified cancer-related proteins (approximately 100) for research programs. Furthermore, these capture reagents must pass performance characterization criteria and be made available as a resource to the scientific community. The minimal performance platforms the affinity reagent must be required to surpass are ELISA-based technologies. Other suggested choices of performance applications that could be validated included Western blot, immunohistochemistry, and immunoprecipitation. In addition, other considerations include quantitative information for affinity reagents (Kd, on-rate, off-rate), the actual binding epitope in order to interpret the quantitative characterization, and application in multiplex platforms such as microarrays. While it is expected that initial development and quality assurance/quality control costs may be comparable to that of monoclonal antibodies, it is intended that production costs of these renewable reagents will be significantly lower.

Phase I Activities and expected deliverables:

- Work with the Clinical Proteomic Technologies for Cancer community, private and public sectors to identify appropriate minimum characterization criteria/validation assays (Commercially available ELISA kits can serve as appropriate tests for performance criteria).
- Generate affinity reagents to at least ten protein targets and demonstrate equivalent or improved performance to ELISA and other affinity-based platforms.
- Present findings to an NCI Evaluation Panel and demonstrate how the capture reagents compare in binding affinity to antibody-based platforms such as ELISA and have improved cost effectiveness and throughput capabilities in production compared to antibodies.
- Research should be proposed with quantitative feasibility milestones.

Phase II Activities and expected deliverables:

- Implement strategy and project plan for a fully functional affinity reagent development platform for at least 100 protein targets developed through the Clinical Proteomics Technology Initiative for Cancer. The reagents should be able to capture the target of interest from complex biological mixtures such as blood, plasma, or tissue. The plan should include comparison with ELISA-based technologies for evaluation of performance criteria.
- Test performance criteria against ELISA and other affinity platforms.
- Work with the Clinical Proteomic Technology Initiative for Cancer programs to integrate capture reagents into the proteomic research platforms.

240 Early Diagnostics Using Nanotechnology-Based Imaging and Sensing

Number of anticipated awards: 3

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

The goal of this project is to develop nanotechnology-based sensors with improved sensitivity and specificity for early detection and post-treatment monitoring of cancer signatures using genomic and proteomic means operating in both *in-vitro* and *in-vivo* environments.

The survival rates from cancer can be dramatically improved *if* the disease is detected early enough. As an example, more than two thirds of ovarian cancer cases are detected at an advanced stage, and the five-year survival rate is 40%. However, if the disease is detected and treated early, when it is still confined to the ovary, the survival rate at five years increases to 90%.

Nanotechnology provides for an attractive alternative towards designing novel *in vitro* sensor platforms for recognition of genomic and proteomic signatures in cancer. The use of nano-object labels: quantum dots, nano-rods, and nano-wires permits for highly multiplex tagging of unknown molecules in a sample and their subsequent tag-by-tag recognition. These recognition can be carried out using optical or electrochemical means. Similarly, label-free sensing modalities can be developed using nano-cantilevers, nanowires, and carbon nanotubes providing for simplification of an assay regime. It is anticipated that these novel assays will exhibit superior sensitivity and specificity and ability to measure multiple signatures (from both genome and proteome), simultaneously. These newly developed sensors in conjunction with integrated sample preparation can facilitate migration of clinical lab tests to the physician's office, near patient, or point-of-care, where rapid access to diagnostic information could lead to more effective and timely medical decisions.

A parallel development which is also expected to contribute to early disease recognition, is related to novel contrast agents based on the nanoparticle platforms such as: magnetic particles, quantum dots, liposomes or dendrimers. These particles loaded with such agent can provide for an improved contrast and resolution of *in vivo* images. What is particularly interesting, is exploration of nanoparticle families and their surface chemistries allowing for a dynamic change of particle properties or their aggregation upon exposure to cancer-specific biomarkers. This property change, which can be subsequently detected through the imaging, for example, provides for an *in vivo* sensor which operates in immediate proximity to the tumor under investigation.

The objective of this program is to demonstrate sensor platform. Nanodevices should be used as: 1) analyte labels, or 2) act as direct sensor/signal transducers in individual or distributed (nanophase film) manner. Initially, sensor would be set-up to work with purified samples in *in vitro* environment, but eventually (Phase II) the sensor should be adapted to carry out analysis of 'real' patient samples. The proof-of-concept for *in vivo* operation will be also expected.

Phase I Activities and expected deliverables:

- Design describing:
  - sensing and transduction methodology
  - particles selected for the solution (their commercial source or synthesis method)
  - expected recognition sensitivities
  - expected false positive rate
- The attributes of the sensing platform should be the following:
  - capability to detect both DNA and protein signatures
  - at least 10-plex detection capability (recognition of 10 independent signatures, simultaneously)
  - detection platform should be 'optics-free' and rely on electronic, magnetic, or other non-optical means of recognition
- Provide proof of concept demonstration using purified sample

Phase II Activities and expected deliverables:

- Provide a working prototype of *in-vitro* sensor system
- Expand number of signature to 50
- Demonstrate sensor sensitivity and specificity for 'real' (acquired from patient) samples. Compare with results from Phase I.
- Demonstrate ability to conduct *in-vivo* sensing solution.

Fast-Track justification:

While not necessary for all offerors, there are specific situations where fast-track funding would be appropriate. Fast-track combines Phase I and Phase II projects into one submission and allows for a faster transition between the phases. If there is a significant amount of preliminary data, or proof of concept demonstration already exists, this approach may result in a faster rate of technology development. A fast-track application requires inclusion of quantitative and specific deliverables in the Phase I portion of the application.

Before Phase II funding is awarded, a progress report towards meeting of the Phase I milestones must be received. Only upon successful evaluation of this report by the program manager will Phase II funding be approved.

241 Multifunctional Therapeutics Based on Nanotechnology

Number of anticipated awards: 3-5

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

The goal of this project is to develop nanodevice-based therapeutic delivery vehicles for high efficacy, low side effects therapies.

Nanoscale devices carrying therapeutic payloads and delivered to a close proximity of tumor *in vivo* can play a significant role in increasing the effectiveness of the treatment while decreasing severity of side effects. Such techniques would be highly relevant, particularly, for organs that are difficult to access because of a variety of biological barriers, including those developed by tumors. For example, nanoparticles are capable of crossing the blood-brain barrier due to their small size and thus are an excellent candidate for non-invasive treatment of brain tumors. Multifunctional nanoscale devices also offer the opportunity to utilize new approaches to therapy, such as localized heating or reactive oxygen generation, and to combine a diagnostic or imaging agent with a therapeutic and even a reporter of therapeutic efficacy in the same nanodevice package.

In conjunction with the development of these devices, local targeting techniques emerge. This process can utilize epitopes expressed on specific signatures of tumor cells or other cellular markers of biological processes such as angiogenic and apoptotic pathways. In molecular oncology, this is more intriguing and potentially useful as a general approach since it allows for targeting of multiple cancers or even more broadly for targeting of multiple diseases. For instance, there are already examples of multi-functional nanoparticles that target vascular peptides, growth factor receptors, transmembrane proteins such as ion channels, and are utilized for both cancer and cardiovascular disease recognition.

The development of an appropriate nanoparticle platform with specific particle size, its physical property providing for particular optical, magnetic, or electrochemical signature, target-specific surface chemistry, and ability to carry the therapeutic payload would lead to the ultimate multi-functional 'find-detect-kill' platforms with superior efficacy.

The goal of this program is to demonstrate *in-vivo* nanodevice-based delivery platform. These devices can take, for example, the form of multi-functional nanoparticles or multi-chamber chips carrying encapsulated drugs. The devices can be administered orally, intravenously, or can be implanted. Two different tracks of technologies will be considered.

TRACK I would focus on discovery and demonstration of novel delivery platform concepts involving, among others:

- novel nanodevices
- novel tumor targeting and concentrations schemes
- novel drug loading and releasing schemes
- schemes enabling crossing the blood-brain barrier.

Phase I Activities and expected deliverables:

- Fabrication technique resulting in the manufacturing of nanodevices with good reproducibility should be developed. The novel use of existing particles acquired from the commercial manufacturer will be also considered under this program.
- *In vitro* (cell culture) demonstration of drug efficacy

Phase II Activities and expected deliverables:

- Demonstration of targeting (multiple biomarkers) and concentration techniques for a specific organ/disease

- *In vivo* small animal drug efficacy demonstration (at least 60 day study with statistically relevant number of animals)

TRACK II would involve further development of existing nanodevice platforms that have demonstrated improved therapeutic efficacy in at least one animal model.

Phase I Activities and expected deliverables:

- Nanodevice manufacturing and scale-up activities

- Additional small animal studies showing improved therapeutic efficacy over non-targeted nanodevices

Phase II Activities and expected deliverables:

- Long term toxicity studies (biodistribution and bioelimination for IV administered nanodevices and biocompatibility for implanted devices)

- IND-enabling studies carried out in a suitable pre-clinical environment

- Initiation of large animal studies

Fast-Track justification:

While not necessary for all grantees, there are specific situations where fast-track funding would be appropriate. Fast-track combines Phase I and Phase II projects into one submission and allows for a faster transition between the phases. If there is a significant amount of preliminary data, or proof of concept demonstration already exists, this approach may result in a faster rate of technology development. A fast-track application requires inclusion of quantitative and specific deliverables in the Phase I portion of the application.

Before Phase II funding is awarded, a progress report towards meeting of the Phase I milestones must be received. Only upon successful evaluation of this report by the program manager will Phase II funding be approved.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

The NHLBI plans, conducts, fosters, and supports an integrated and coordinated program of basic research, clinical investigation, and trials, observational studies, and demonstration and education projects. The Institute's mission includes studies related to the causes, prevention, diagnosis, and treatment of heart, blood vessel, lung, blood, sleep disorders, and blood resources management. Studies are conducted in its own laboratories and by other scientific institutions and individuals supported by research grants and contracts. The NHLBI SBIR program fosters basic, applied, and clinical research on all product and service development related to the mission of the NHLBI.

This solicitation invites proposals in the following areas.

035 Ultrasonic Wave Transmitter, Transmission Line and Receiver for Interventional MRI

(Fast-Track proposals will be accepted.)

At the present time, signals from electronically active devices used within an MR scanner are transmitted out of the scanner on coaxial cables. This includes signals from "marker" coils on interventional devices such as catheters and guidewires. These long transmission lines couple with the transmitted RF which can potentially cause heating in the patient. If the conductor length can be made lower than a quarter of the transmitting wavelength, the heating problem can be eliminated; but, this length is approximately 30 cm within the body and the average length of intravascular catheters is about 1 meter. A non-conductive transmission line was designed to carry RF signals to eliminate this heating problem. In this design, a conductive coil at the distal tip of the catheter receives RF signals emitted by the tissue. The received signal reaches the micro piezoelectric transducer (MPT) and the MPT converts the RF signal into an ultrasonic wave. A custom designed acoustic wave guide transmits the signal until it reaches the proximal end of the catheter. At this point another MPT receives the ultrasonic wave and converts it back to an electronic RF wave, and after amplification of the signal it reaches the scanner receiver for MR image reconstruction. This will be the first application of ultrasonic waves to visualize interventional MRI catheters. The most challenging part of this project is miniaturizing the technology to fit inside a 0.035" outer-diameter catheter. To manufacture the first

prototype, we need acoustic transducers, transducer electrodes and custom designed acoustic wave guide defined by using photolithographic techniques.

The Phase I application should provide proof of concept for conversion of the RF signal to acoustical domain, and transmission of the acoustical signal in a wave-guide. In this phase, available materials will also be evaluated in terms of performance and efficiency. Iterative designs will consider available materials and fabrication methods that may be suitable for later phases. The electrodes on the transducer will be patterned using microelectromechanics techniques such as photolithography. Tools will be developed to align and attach the transducers and the wave-guide. Phase I will yield a functional prototype.

The Phase II application will translate the Phase I findings into a clinical grade device. The wave-guide will be similar to the final product in terms of acoustical properties. The whole device will be composed of two transducers, an acoustic wave-guide and a low noise amplifier. The project includes in vitro and in vivo testing.

036 Ultrafine Magnesium Biodegradable Stents for Orphan Disease Applications

(Fast-Track proposals will be accepted.)

Metallic stents have revolutionized catheter-based treatments for coronary artery obstructive atherosclerosis, by stabilizing arterial lesions after percutaneous coronary balloon angioplasty and by dramatically reducing post-angioplasty stenosis. For certain less-common ("orphan") applications, conventional stent implantation is not viable. Such applications include implantation in children whose target arteries are expected to grow, in which arteries outgrow the endoprosthesis; implantation in arteries that cross joint flexures, in which permanent implants cause chronic mechanical injury and endoprosthesis failure; and implantation under imaging guidance other than X-ray fluoroscopy, in which conventional ferrous alloys interfere with imaging.

Biodegradable (temporary) magnesium-alloy stents have been developed and tested for coronary and noncoronary artery implantation, but have demonstrated unacceptably variable biodegradation associated with unacceptably high post-implantation arterial restenosis. However, the alloys employed for these devices suffer large crystal structure and substantial crystal inhomogeneity that are thought to contribute to embolization and device failure during biodegradation.

Ultrafine crystal magnesium alloys can be produced by rapid solidification processes. When manufactured with micron-scale crystal structure, such alloys promote uniform biodegradation, precluding fragment embolization and device failure.

Metallic stents manufactured from such alloys should have acceptable mechanical characteristics (strength, ductility comparable to contemporary MP35N, cobalt chromium, and 316L steel coronary stents marketed in the US). The stents should have uniform micron-scale (<3μm) crystal grains to provide uniform controlled biodegradation (biocorrosion) and biocompatibility (including galvanic) characteristics suitable for the orphan applications described above, and should be MRI safe and MRI compatible. The most challenging part of the project is extrusion and then laser cutting of suitable rods for stent manufacture.

Such devices are needed to conduct proof of principle experiments, for example, in growing juvenile large mammals, and/or in arteries spanning joint flextures in animals permitted prolonged mobility, and/or under imaging guidance other than X-ray fluoroscopy such as real-time MRI.

In the Phase I application, biodegradable and biocompatible magnesium alloys will be generated with uniform micron-scale crystal grains. The alloys will have malleability and strength suitable for vascular stents that biodegrade in controlled fashion between weeks or months. In this phase, a proof of principal stent is designed and prototyped. This phase also includes in vitro cytotoxicity and in vitro hemolysis as well as in vivo biocompatibility testing.

In the Phase II application clinical grade vascular stents will be manufactured in phase II, including suitable cutting and electropolishing. This phase also includes in vivo proof of concept in large mammals including deployability, radial strength, and biodegradation.

037 Critical Technologies for Ventricular Assist Devices

(Fast-Track proposals will be accepted.)

The options for long-term survival for the 50,000-100,000 late-stage heart failure patients in the United States are very limited. Only 8% will survive two years without a heart transplant or a ventricular assist device (VAD). Because the heart transplant

donor pool in the United States is less than 2,500/year, VADs are the only realistic option for most of the affected population. However, due to the prohibitive morbidity and costs associated with the devices, only about 2,000 receive VADs each year as permanent or “destination” therapy. If the risk/benefit ratio of mechanical circulatory support therapy is substantially improved by scientific advances which successfully reduce the multiple associated late complications, destination therapy would become a much more viable option for patients with late-stage heart failure.

The goal of this proposal is to develop novel technologies to successfully mitigate the most prevalent serious adverse events associated with chronic mechanical circulatory support: thrombosis, hemorrhage, neurocognitive impairment, and infection. Examples of appropriate goals include the development of techniques to deliver anti-thrombotic or thrombolytic agents targeted to VAD surfaces or (2) heparin or anti-platelet embedded surfaces or coatings to inhibit thrombogenesis.

Phase I applications should address initial development and feasibility testing of a novel technology which can be applied to existing or new circulatory support devices to mitigate thrombosis, hemorrhage, thromboembolism, and/or infection associated with these devices.

Phase II applications should be focused on completing the development of the technology such that it can be readily incorporated into circulatory support devices. The work is expected to include in vitro and in vivo studies to demonstrate effectiveness.

038 Production of Generic Modified Hemoglobin

(Fast-Track proposals will be accepted.)

The quest to bring hemoglobin-based oxygen carriers (HBOCs) to market began well over a half century ago. Recent clinical experiences in the U.S. with candidate HBOCs however have not resulted in the availability of licensed products primarily due to toxicities observed in a number of clinical trials. While the past decade has seen significant efforts from the commercial sector of product design and evaluation, a true understanding of the basic science underlying the observed toxicities and basic physiology of hemoglobin-based solutions is lacking. Fundamental research studies are clearly needed but it is extremely difficult if not impossible for some investigators to obtain sufficient quantities of these products to conduct research studies. This situation is due to a variety of reasons including limited availability of products or the proprietary nature of certain commercial products. For knowledge in this field to grow at a more rapid rate, there is a fundamental need for a source of HBOCs which would be available to support and accelerate research efforts in this area. The availability of such products will benefit those investigators who have had a long standing interest in addressing basic research questions as well as new investigators and investigators who may have never worked in this area but would do so if HBOCs were available.

The goal of this solicitation is the development and production of generic modified hemoglobin(s) for research purposes which would be made available to the scientific community interested in pursuing research studies in this area. The homogenous raw materials must be well defined in their physico-chemical characteristics (e.g., Hb/metHb, P50, MW profile, pH, electrolytes, stability, endotoxin test, viral inactivated, etc), produced under good manufacturing practices (GMP), be uniform from batch to batch, and certified by quality control. The products may range from solutions of native hemoglobin (A0), stroma free hemoglobin (SFH), to a variety of modified forms. The successful offeror must have a high quality production facility available, know protein molecular, biochemical and extraction techniques and have experience in biochemical modifications.

Phase I applications should focus on the development of a well-characterized generic hemoglobin solution(s) for research purposes. Investigations in this phase shall involve laboratory bench and early scale-up studies.

Phase II applications shall focus on scale-up and production of a HBOC(s) under GMP. Enough product(s) shall be produced to satisfy the research needs of U.S. investigators interested in pursuing fundamental research studies on HBOC.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

The NIAAA supports research on the causes, prevention, control, and treatment of the major health problems of alcohol abuse, alcoholism, and alcohol-related problems. Through its extramural research programs, the NIAAA funds a wide range of basic and applied research to develop new and/or improved technologies and approaches for increasing the effectiveness of diagnosis, treatment,

and prevention. The NIAAA also is concerned with strengthening research dissemination, scientific communications, public education, and data collection activities in the areas of its research programs.

This solicitation invites proposals in the following area:

029 Development of Correlational Alcohol-Relevant Database from Mouse or Rat Transcriptome and Proteome

(Fast-Track proposals will be accepted)

The mouse and rat have become the foundation of genetic and other preclinical studies in alcoholism and related research areas (Goldman, D., Crabbe J. Prog. Neuropsychopharm. BioI. Psych. 10: 177-189, 1986). Alcoholism researchers have well exploited mouse and rat models for genetic analysis of alcohol-related behaviors and to understand alcohol's actions in brain (Tabakoff B., Hoffman, P.L. Alcohol Res. Hlth 24: 77-84, 2000). Recent technology allows for large-scale examinations of the mouse and rat transcriptome and proteome (Doerge, R.W. Nature Rev Genetics 3: 43-52, 2002; Chakravarti, D.N. et al. BioTechniques Suppl. 1: 4-15, 2002). A recent NIAAA Workshop on Proteomics focused attention on how these technological advances can further the research on the etiology of alcoholism and alcohol-induced tissue damage, and how they can be used to identify medications targets for alcoholism.

To justify large-scale investment in support of proteomic research projects, several important issues can be addressed initially through a contractual mechanism to establish "proof of concept" and the utility of integration of proteomic information with gene array and genomic data in studies of alcoholism and alcohol-related organ damage.

Little or no data have appeared in the literature correlating transcriptional data to protein levels and measures of post-translational modifications in mammalian species. Knowing the relationship between transcriptional data and protein levels, particularly in experiments with ethanol, is of significant importance since ethanol can perturb cellular systems at various levels to cause organ damage or generate neuroadaptation leading to tolerance and dependence on ethanol. Data also need to be collected for calibrating the performance of custom arrays and commercial products such as the Affymetrix "chip" arrays. Proprietary information issues, periodic changes in commercial chip properties and commercial company closures make long-term experiments using commercial devices inappropriately risky for purposes of comparison and development of sound databases.

The purpose of this announcement is to generate a contractual agreement with a group possessing a demonstrated capacity to perform, analyze, store and distribute transcriptional and translational data utilizing animal and cellular models of high relevance to alcohol research. Transcriptional data should be obtained on either "custom" arrays or commercial platforms (such as Affymetrix arrays) containing a minimum of 12,000 gene probes. Protein translational information should be obtained with the most current techniques that can examine a vast array of cellular proteins simultaneously. Informatics expertise and equipment needs to be available to the contractor to make definitive comparisons between the transcriptional and proteomic information. The contractor should have the means in place to allow access to this database by the alcohol research community. Contractors from different small businesses have the option to team up with one another to apply for a contract together. The potential commercial product (e.g., database) should be partly accessible to the public and partly to generate revenues. If more than one company collaborate together to achieve this goal, they should work out a priori agreement for sharing the revenues.

The following are examples of experimental systems and techniques (not exclusive of others) that should be considered for use by the contractor:

a) Utilize selected lines of mice or rats which, for instance, differ in their development of acute functional tolerance to alcohol or preference to alcohol. Assay relevant tissues at different exposure time points.

b) Utilize mouse or rat models to profile gene expression or proteomic changes associated with alcohol-induced organ damage.

c) Utilize transgenic or knockout mice in which an alcohol-sensitive signaling molecule (protein kinase or adenlylyl cyclase) has been overexpressed or knocked out in relevant organs of animals.

d) Examine gene expression in whole brain or targeted brain areas (e.g., hippocampus, amygdala, striatum, prefrontal cortex and

cerebellum) using commercial or custom arrays which simultaneously examine expression of >12,000 genes.

e) Examine changes in the proteome in the animal brains and other relevant organs using state of the art proteomic techniques, including laser desorption, *"in situ"* trypsinization of proteins on two-dimensional gels, creation of protein blots for archiving experiments, and mass spectroscopic analysis of proteins for identity and quantity.

f) Use state-of-the-art informatics and statistical techniques for comparing transcriptional and translational events and profiles, focusing on identity of gene products and description of functional characteristics of known gene products (mRNA and protein).

g) Discover alcohol-induced changes and inherent predisposing elements (mRNA and protein) to alcohol's effects that are not yet catalogued and characterized in genomic and proteomic databases.

Phase I: Set up study using custom or commercial array (e.g., Affymetrix, etc) to profile gene expression at different concentrations of ethanol exposure in the relevant organs (brain, liver, etc.). Set up proteomic analysis for the same tissues under the same ethanol concentrations as in the genomic analysis. At the end of Phase I, it is anticipated that at least one set of analyses will be performed, analyzed, and stored in the database.

Phase II: In the second year, results of the initial survey will be expanded to analyzing at least 12,000 genes and a full complement of corresponding proteins. A database, or databases, containing this transcriptional and proteomic data with affected genes and proteins will be established and made available for access by the alcohol research community.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD)

The NICHD conducts and supports research and research training on biological and behavioral aspects of human development. Primary program areas include: reproduction and population studies, pregnancy, perinatal biology, maternal and infant well-being, developmental and reproductive immunology, congenital defects, developmental biology, nutrition and growth, human learning and behavior, learning disabilities and developmental disabilities, AIDS and HIV, and medical rehabilitation.

For additional information about areas of scientific interest to the NICHD, please visit our home page at http://www.nichd.nih.gov/.

Total costs for the following NICHD contract topic is capped at a maximum of $100,000 for Phase I and $750,000 total costs for Phase II.

This solicitation invites proposals in the following area for the topic listed below:

022 Development of a User-based Information System for Mobility Needs

(Fast-Track proposals will not be accepted.)

Because an ever-increasing number of new and improved state-of-the-art mobility products are appearing in the marketplace, consumers with disabilities are finding it increasingly difficult to know exactly what products are currently available and which products will meet their needs.

Mobility devices are essential for expanding the access of persons with functional disabilities, encouraging more active participation, and improving psychosocial lifestyles. Under the circumstances there is a significant need for advice in helping disabled people to evaluate the relative merits of available products in making it easier for them to get around - both indoors and out. It is also important to recognize that some aspects of device utility only become apparent with consumer usage and experience.

Most consumers value professionally acquired product information relative to sustainability, usability, flexibility, reliability, consumer satisfaction and of course cost prior to purchase. This is critical because current healthcare constraints generally limit opportunities to revise purchase decisions down the road. Moreover, consumers with newly acquired or late-onset conditions may be just coming to grips with the implications of their incapacities and long-term needs and seek help in making informed decisions.

In summary, there is an urgent need for easy to access, ecologically valid evaluation standards and professionally prepared reports on products which have been or soon will be marketed to meet the evolving needs of the world's functionally impaired consumer population.

The purpose of this solicitation is to establish a user-friendly resource that will provide practical information about state of the art mobility product(s). To meet this goal the offeror should initially focus on a specific class of mobility device (e.g., manual wheelchairs or scooters) and a particular population (e.g., adults or children) in order to develop an information reporting system (e.g., community based product trial, interview system, digital clips of technology in home use, web-based, or other). Letters of support from the major constituent groups (e.g., manufactures, consumers, durable medical equipment vendors, scientists and engineers, etc.) involved should accompany the application.

Phase I:

To be responsive to this solicitation a feasibility proposal should address content specifications (e.g., what data will be obtained and how) including a rating system and implementation plan to illustrate how the information obtained will be displayed. It should also include methods for making the assistance of the system known to the widest possible number of people with mobility limitations (e.g., appropriate list serves, large mailings to orthopedic doctors and /or physical therapists, consumer publications aimed at disabled people, etc.). Possible methods of minimizing costs of printing, packaging and postage should also be addressed.

Areas the proposal should convey include but are not limited to the following:

a) Ability to recruit and gain assistance of appropriate organizations (e.g., disability organizations, durable equipment vendors, consumer groups, manufacturers, university faculty, etc.);

b) Knowledge of end-users needs;

c) Knowledge of existing technology information systems and their strengths and weaknesses;

d) Preparation of a report detailing the design and implementation of the data gathering system, including a theoretical and methodological bases for the evaluation;

e) Development of a prototype data gathering system for consumer ratings;

f) Discussion and rationale for selection of a particular mobility device.

Phase II:

Using the selected mobility product, the contractor shall be expected to create a reference system that can be easily accessed from various sources such as a home computer, list services, community library, doctor's offices and rehabilitation hospitals for people seeking to regain a greater measure of self-sufficiency. The resultant system shall be expected to contain as a minimum the following:

a) Implementation strategy and project plan for a fully functional user-based information system;

b) Ability of a metric system chosen to define the quality of the device(s) in areas such as accessibility, durability, flexibility, functional reliability, mobility, etc.;

c) Fully working software to implement the Phase I data gathering system for consumer ratings of the chosen mobility device ;

d) Documentation of the software code, programming interfaces, and hardware requirements;

e) A study ability to capture data from the person with a mobility limitation and the system's ability to display aggregate data;

f) Demonstration of data security system;

g) Development of a self-sustaining business model.

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

NIDA's mission is to lead the nation in bringing the power of science to bear on drug abuse and addiction, through support and conduct of research across a broad range of disciplines and by ensuring rapid and effective dissemination and use of research results to improve prevention, treatment, and policy.

This solicitation invites proposals in the following areas:

076 Development Of Science Literacy Materials Or Programs

(Fast-Track proposals will be accepted.)

The purpose of this proposed SBIR project is to develop projects or programs to improve science literacy among the general public. For many years public science literacy has remained low. Yet it remains important to the mission of NIDA that the general public and other groups are scientifically literate. It is particularly important to NIDA that all

members of society understand the role of science, biology, and technology as they relate to neuroscience and drug abuse and addiction research. There is a lack of public understanding of behaviors that increase the risk for drug abuse, the use of animals in drug abuse related behavioral and biomedical research, and the necessity for basic research to make progress toward improving health. Furthermore, there is a substantial misunderstanding about the nature of addiction as a biologically based brain disorder. To address all of these issues, it is imperative that efforts be made to educate the general public and other groups about the science of addiction.

Therefore to address these issues this contract solicitation seeks innovative projects or programs that will substantially improve scientific literacy among the general public. Programs or projects must seek to improve general scientific literacy with a specific focus on drug abuse related research. Programs or projects should be directed to increasing the knowledge of the general public of scientific terms, concepts, reasoning, as well as their ability to understand scientific public policy issues. An evaluation component must be included that can provide useful and accurate information on the efficacy of the program or project.

Phase I should include studies to determine the best format, studies that demonstrate feasibility, and the development of a prototype.

Phase II should include continued formative evaluations to guide the development of the program or project, development of the program or project, and a summative evaluation to determine the project/program's efficacy in improving science literacy.

082 Development of Novel Drug Delivery Systems for Treatment Medications

(Fast-Track proposals will be accepted.)

NIDA is seeking SBIR contract proposals on innovative and novel dosage form development to improve the effectiveness and/or minimize the abuse potential of therapeutic agents for drug abuse/dependence. The pharmacotherapeutic agents of interest include, but are not limited to, buprenorphine and delta-9-tetrahydrocannabinol (THC). Buprenorphine has been approved for the treatment of opioid dependence. Sustained-release formulations that reduce the dosing frequency to once a week or once a month would be expected to improve compliance thus effectiveness of treatment. THC has been shown to alleviate marijuana withdrawal symptoms and thus has potential for treating cannabinoid dependence. However, the bioavailability of THC administered orally is poor and variable. In addition, it also requires drug administration several times a day. Formulations to improve bioavailability and/or to reduce dosing frequency would be expected to improve the therapeutic effectiveness of THC.

In Phase I, the contractor is expected to demonstrate the feasibility of the dosage form by formulating a prototype dosage form based on biopharmaceutical and pharmaceutical rationale. In Phase II, the contractor will carry out pharmacological, toxicological and pharmacokinetic evaluations. The contractor is expected to provide a GMP scale-up of a stable dosage form with acceptable *in vitro* and *in vivo* bioavailability in animal models and/or in humans.

085 Metabolomics in Drug Abuse Research

(Fast-Track proposals will be accepted.)

NIDA is seeking proposals to develop novel metabolomics technologies to conduct pathway and network investigation of biological systems relevant to the mechanisms of drug addiction and to the discovery of biomarkers for assessing the efficacy of treatment for drug addiction.

Metabolomics is the identification and quantification of all molecules of a cell or organism, their regulation, metabolic pathways, activity and response under normal and abnormal conditions. Metabolomics thus could be used to develop metabolic profiling of normal or healthy subjects as well as subjects under the influence of substances of abuse or undergoing drug rehabilitation.

Phase I proposal should demonstrate the feasibility of developing new metabolomics technology and phase II should focus on the application of this technology in drug abuse research or treatment.

086 Marketing Evidence-Based Prevention Interventions for Substance Abuse and Related HIV Prevention

(Fast-Track proposals will be accepted.)

The purpose of this SBIR contract is to stimulate the development of marketing technologies for the large scale dissemination of evidence-based drug abuse and drug related HIV preventive interventions. Over

the past 30 years many of drug abuse and drug related HIV prevention programs and practices have been rigorously tested using randomized control trials. Many of these interventions have been demonstrated to be both efficacious and effective. Despite the success of the research, few evidence-based interventions have been adopted and sustained on a wide scale basis. There are many explanations for this situation; however one of the most powerful is the lack of adequate marketing or marketing infrastructures for the dissemination for evidence-based substance abuse and related HIV interventions to schools, communities, health centers, community based organizations and so forth.

Thus, strategies for marketing evidence-based drug abuse and HIV prevention programs and practices need to be developed and implemented. Critical features that need to be considered include for example the processes associated with decision making, adoption, financing, management and utilization of scientifically validated interventions by service systems under controlled, uncontrolled or uncontrollable conditions while maintaining the quality and integrity of the original practice.

Previous PRB SBIR contracts have focused on a variety of approaches to prevention intervention research. This solicitation seeks research in on marketing research specific to drug abuse and HIV prevention programs and practices. Phase I would explore the practicality of the potential product through development and pilot testing of strategies. If proven feasible, Phase II would develop and the test the strategies prior to dissemination.

087 Development of State-of-the-Art Mechanisms for Epidemiological Research

(Fast-Track proposals will be accepted.)

The purpose of this proposed SBIR project is to encourage the development of state-of-the-art mechanisms to facilitate the use of Geographical Information Systems (GIS) in community epidemiology studies (for example Community Epidemiology Work Groups) and other drug abuse research.

The questions NIDA seeks to answer in epidemiological investigations are often inherently spatial in nature, for example, ‘How do neighborhood contextual factors influence the prevalence of cocaine users?’, ‘How are overdose mortalities related to potential sources of environmental exposure and the location of treatment resources?’, and ‘Are rates of methamphetamine use elevated around production outlets?’ Such investigations require that spatially referenced data concerning demographic characteristics of the population, their health, and the environment in which they live, be combined in a common geographical framework for analysis. Geographical Information Systems provide one way of doing this.

The role of GIS in public health management and practice continues to evolve. Application of this technology is an important step towards better understanding drug abuse issues and their inherent complexities. The ability to evaluate geospatial information provides a unique perspective of public health issues such as emerging and shifting epidemics, the utilization of treatment services, and rapid assessment of the impact of incidents ranging from natural disasters to bioterrorism. When used alongside more traditional epidemiological techniques, GIS provides epidemiologists the ability to address new questions, refine, or enhance existing analyses. This initiative encourages the development of both software and hardware to facilitate the development of GIS interfaces, database management, visualization, and innovative spatial analysis capabilities.

Phase I would involve the development and pilot testing of the new technology. Phase II would involve widespread testing and the development of manuals and other support materials.

088 Automation of the Development of Electronic Data Capture (EDC) System for Clinical Trials Data Collection and Management

(Fast-Track proposals will be accepted.)

Information is captured in clinical trials by using either electronic or paper Case Report Forms (CRFs), which consist of multiple pages and sections. Each section is referred to as an individual CRF. It is not unusual for a trial protocol to require 20 CRFs. Based on the individual CRFs, the Electronic Data Capture (EDC) system is developed for users to collect data elements for data management and data analysis. Each CRF has a data dictionary, which specifies the characteristics of each data element, such as data name, data type, length, valid response, logic checks, etc. Currently, the time required for a programmer to develop an EDC system is around two to three days per CRF. Therefore, it would

take more than two months to program the EDC for the average trial. .

This SBIR project is to develop an automated system, called Automated Development of EDC (AD-EDC) System, which can read the information specified in the data dictionary and create the corresponding EDC system within 10 minutes for one CRF.

In addition to data collection, the EDC system shall be a web-based application that can (1) perform the real-time data quality control and (2) meet the federal government's security requirements and auditing requirements. This AD-EDC system should run within the UNIX and Microsoft Windows environments. The database should be compliant with CDISC (Clinical Data Interchange Standards Consortium) standards.

Phase I (6 months): Analysis of the feasibility of the AD-EDC system concept.

Major tasks are to (1) identify system requirements, (2) perform risk analysis, (3) develop a high-level system architecture, and (4) provide a cost benefit analysis report. An assessment by the NIDA's Clinical Trials Network will be performed for the decision of "Go" or "No Go" of Phase II.

Phase II (24 months): Develop a prototype to prove the concepts of operation**.**

Major tasks are to (1) select a historical protocol and analyze the EDC system development life cycle, CRFs design and format, specifications of data dictionary, user requirements, system requirements, database development, audit trail, and data queries, as well as (2) develop a prototype of AD-EDC system to prove the operational concepts.

Phase III : Move the Phase II innovation from the prototype to commercial product.

089 Development of Practical Training Materials for Evidence-Based Treatment

(Fast-Track proposals will be accepted.)

States have initiated the requirement that community treatment programs provide evidence-based treatment or risk losing their public funding if they don't comply. The onus is on the publicly funded program to provide their staff with training in evidence-based treatment modalities. Current staff training opportunities in evidence-based treatments are expensive and frequently require repetition because of high rates of staff turnover. The level of staff training and education varies across agencies. Certification in evidence-based treatment has not been standardized. Externally presented training is not timely or efficient. Computers with Internet capabilities are not always available for staff learning opportunities. It is important to offer alternatives to the delivery of training that are easy for staff to access and that meet requirements to provide evidence-based treatment.

This SBIR project is to develop practical non-computer as well as interactive self-administered computer versions for training counseling staff in evidence-based drug abuse treatments with competency testing to meet local and state requirements for certification, such as, motivational incentives, motivational interviewing, cognitive-behavior therapy, and other proved therapies.

Projects or programs should be directed to increasing the knowledge and understanding of evidence-based treatment methodologies and in a cost effective manner. Training materials should be easy to read, contain an approved curriculum, and incorporate different testing strategies to determine competency. Programs should be self-directed and allow for frequent interruptions or use offsite. These may include textbooks, CDs, DVDs or other materials that allow for self-paced study.

Phase I (six months): An in-depth evaluation of current training materials that are evidence based. Determine which have been validated and have competency testing. Identify effective formats and methods of delivery. Assess the requirements for successful utilization.

Phase II (24 months): Select one or two evidence-based therapies for the development of training programs. Design and evaluate the efficacy of the selected programs in improving the delivery of evidence-based treatment services.

Phase III: Develop print and/or audio/visual training programs for commercialization.

090 Develop a Real-Time fMRI Feedback System that Allows Drug Abusers to Control their Cravings and Urges and/or Increase their Self-Control of their Drug Taking

(Fast-Track proposals will be accepted.)

Data from recent research have shown that pain patients, who are provided real-time neural feedback, via fMRI, of their own brain activity, can control levels of brain activity in discrete brain regions. Further, these changes in brain activity

were found to have a functional impact on the subjects; i.e. they were able to reduce the level of pain they perceived.

Under this solicitation, we are seeking the development and demonstrated efficacy of a protocol for using fMRI to reduce drug abuse by allowing individuals to control the activity in specific brain areas associated with drug seeking. This technology could be used to help patients manage urges to take drugs by inhibiting the neural substrates associated with craving or drug seeking. Alternatively, this technology could be designed to allow patients to increase activity in areas of the brain associated with executive function and self-control, which, in turn, could help reduce or eliminate abuse of drugs. A combined approach would also be acceptable, where multiple brain areas are activated and/or inhibited by the subjects, with the goal of reducing or eliminating drug abuse. Lastly, an approach that reduces pain while controlling the potential for drug abuse in patients receiving prescription pain medications is sought.

Phase I would involve developing this technology and testing its feasibility and efficacy in a small pilot study. Phase II would involve further development and iterative testing, in applied clinical settings, of those technologies that proved efficacious in Phase I.

091 Design and Synthesis of Treatment Agents for Drug Abuse

(Fast-Track proposals will be accepted.)

The purpose of this contract is to design and synthesize novel compounds intended specifically for the treatment of substance abuse including cocaine, methamphetamine or cannabinoid abuse. The classes of pharmacotherapeutic agents include, but are not limited to, compounds interacting with corticotrophins, cannabinoid, biogenic amines, GABA, and glutamate systems. The design and development of antibodies as immunopharmacotherapy treatments for drug abuse will also be of interest.

In Phase I, the Contractor will design and synthesize new entities as potential treatment agents and carry out *in vitro* and/or *in vivo* pharmacological screens. In Phase II, the Contractor will perform pharmacological and toxicological evaluations and select lead compounds as potential clinical candidates.

092 Mechanisms and Methods to Maximize Data Utilization

(Fast-Track proposals will be accepted.)

The International Program of NIDA supports research, training, and education activities that address the global impact of drug addiction. The purpose of this project is to further define and develop strategies to capitalize more fully on existing data in order to provide useful scientific information for scientists, clinicians, and policy makers. Therefore, NIDA is interested in projects that address access, analysis, publication, and dissemination of information in extant data. In the United States and many other countries, significant resources are expended to collect data on drug use patterns, consequences of use, etc. However, it is also the case that these data are rarely fully analyzed and evaluated for findings that could impact policies and programs. Such secondary data analysis can be an extremely cost effective and valuable use of resources. Also, while the strategies to address the international phenomenon of drug addiction need to be empirically driven, there are limited funds to support original international drug abuse research which subsequently increases the importance of secondary analyses of existing data sources particularly in low- and middle-income countries. The mechanism to expand the use of existing data sources that can inform policy is likely be multifaceted and may include: identification of existing data sources, provision of training in secondary data analyses, and interpretation of data analyses for making evidence-based decisions. The focus of the research can address any component of drug use, abuse and addiction that is within NIDA's research portfolio.

Phase I could include the preliminary stages of identifying existing data sources, providing training in secondary data analyses and interpretation of data analyses. Phase II would include full development and testing of the above.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS)

Human health and human disease result from three interactive elements: environmental exposures, individual susceptibility and time. The mission of NIEHS is to reduce the burden of human illness and dysfunction from environmental exposures by understanding each of these elements and how they interrelate. NIEHS achieves its mission through multidisciplinary biomedical research programs,

prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach. This Small Business Innovation Research Program (SBIR) uses a combination of research and technology transfer in order to develop new products that will aid the mission of NIEHS.

This solicitation invites SBIR proposals in the following areas:

101 Gene Expression and Molecular Imaging to Identify Early Biomarkers and Staging of Lung Cancer Following Environmental Exposures

(Fast-Track proposals will be accepted.)

Lung cancer is the leading cause of cancer death world wide, and the need to develop better diagnostic techniques and therapies is urgent. Mouse models have been utilized for studying carcinogenesis of human lung cancers, and many of the major genetic alterations detected in human lung cancers have also been identified in mouse lung tumors. The importance of mouse models for understanding human lung carcinogenic processes and developing early diagnostic techniques cannot be overstated. Advances in gene expression profiling and molecular imaging are providing unique opportunities to better define the early stages of cancer. To date, only a few gene expression studies have been performed in mouse lung tumor models and showed similar molecular pathways to human lung tumors. However, no one has focused on the early stages of lung cancer. One goal of the studies developed under this proposal is to identify key genes and molecular pathways related to the stepwise tumor progression from normal, hyperplasia, adenoma, to carcinoma. The focus should be on performing gene expression analysis on the early stages of lung cancer using microarray technology to identify predictors and molecular biomarkers of effect following environmental exposure. While new approaches in gene expression profiling have taken place over the past decade, parallel advances have occurred in molecular imaging which characterize and measures molecular events in living animals with high sensitivity and spatial resolution. A second goal of this proposal is to use the information from the gene expression profiles to design molecular probes for optical imaging. Imaging these molecular events is achieved by using innovative imaging agents including “smart sensor probes” that can be activated upon interactions with their biological targets. Therefore gene expression profiling will identify key molecular events from which will be developed molecular imaging probes allowing the early detection of lung cancer in vivo. The findings from these studies will further allow for reduction in costs and in the use of animals in research and provide potentially important diagnostic information for human lung cancers.

102 Quantitative Analysis of Protein Expression in Paraffin Embedded Rodent Tissues

(Fast-Track proposals will be accepted.)

Transcriptional microarray analysis can provide data the activity of all the genes in a tissue relatively quickly. Microarray technology is usually based on RNA isolated from tissue homogenates and thus spatial information on which regions or cells in a tissue are involved is not captured. Anatomic pathology is a critical component of this molecular technology because it allows an association between gene expression changes and specific cellular and regional changes within the tissue. However, transcripts do not provide direct information on protein changes which are not always reflectively of gene message because of post-translational modifications and other factors. Thus the goal of this contract would be to develop fluorescence-based methods that can be used to quantify protein expression at the cellular and sub-cellular level in paraffin embedded tissues. This technology is currently being applied to analysis of human cancer biopsies both to determine prognoses and in the selection of potential cancer therapies. This technology has the potential to be useful in the support of toxicology evaluations and allow the direct quantification of protein levels in tissues following chemical exposure. This technology will provide a bridge between gene expression changes and histopathology results that are currently part of many studies. It is predicted that the ability to quantify multiple proteins on tissue sections will provide an efficient and economical method to identify mechanisms leading to toxicity and carcinogenicity.

103 Development of an ELISA for Measuring Serum Levels of NAG-1/MIC/GDF15

(Fast-Track proposals will be accepted.)

Chronic inflammation plays a causative role in many cancers. NAG-1/MIC/GDF15 is a member of the TGFβ super family that has anti-cancer as well as anti-inflammatory activity. The expression of this

protein is increased by a number of anti-inflammatory and chemo-preventive drugs including COX inhibitors and dietary agents. The protein is formed as a pro-protein, cleaved and secreted as a mature dimer that has been detected in the serum of cancer patients. A polymorphism has been identified that changes the basic amino acid histidine to the acidic amino acid aspartic acid in position 6 of the mature protein. This H6D polymorphism in the NAG-1 gene is associated with prostate cancer. The goal of this contract is to develop an ELISA kit to measure the plasma levels of NAG-1 or the H6D mutant which would aid the investigation of the importance of this protein in a number of diseases. Currently PSA, prostate specific antigen is used as a tool for the early detection of prostate cancer. However, elevated PSA is also found in benign prostatic disease and there is a critical need to improve the specificity of PSA testing. Therefore, the potential increase in the reliability of prostate cancer diagnosis based on combined screening involving an ELISA for NAG-1/H6D and an ELISA for PSA in serum needs to be investigated.

104 Identifying Biomarkers to Predict Renal Disease in Rodent Cancer Bioassays

(Fast-Track proposals will be accepted.)

The National Toxicology Program (NTP) is responsible for designing, conducting, and evaluating toxicological tests on agents that are deemed important to the public health. Among these tests, the toxic and carcinogenic potential of an agent is assessed with a standard two-year rodent bioassay. Renal toxicity and/or neoplasms are commonly observed in the two-year bioassay, particularly the rat. The two-year bioassay is expensive and time-consuming, requiring nearly lifetime exposures in mice and rats. Since there are approximately 80,000 chemicals registered for commercial use in the United States and 2,000 more are added each year, applying the rodent bioassay to all chemicals of concern is clearly impossible. Transcriptional microarray analysis, 2-D gel proteomic studies, and NMR-based metabonomic studies have proven to be useful in predicting acute toxicological endpoints such as nephrotoxicity. However, few studies have utilized these technologies for predicting chronic renal endpoints. The aim of this effort would be to determine whether transcriptomic, proteomic, and/or metabonomic biomarkers can be identified in renal tissue or urine following a subchronic exposure that are predictive of tumor formation or non-neoplastic toxicity in a two-year bioassay. Transcriptional, proteomic, or metabolic biomarkers that are relatively inexpensive to measure in renal tissue or urine will provide an efficient and economical method to identify potential renal toxicants and carcinogens prior to widespread use. The findings may also identify useful biomarkers of human exposure for individual or classes of agents.

NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH)

The mission of the National Institute of Mental Health (NIMH) is to reduce the burden of mental illness through research on the mind, brain, and behavior. Mental disorders constitute an immense burden on the U.S. population, with major depression now the leading cause of disability in the U.S., and schizophrenia, bipolar disorder, and obsessive-compulsive disorder ranked among the ten leading causes of disability. NIMH also takes the lead in understanding the impact of behavior on HIV transmission and pathogenesis, and in developing effective behavioral preventive interventions. The NIMH conducts a wide range of research, research training, research capacity development, as well as, public information outreach and dissemination to fulfill its mission.

This solicitation invites proposals in the following areas:

057 Development of Iterative Continuous Clinical Improvement (ICCI) Models for Mental Disorders Utilizing Clinical Trials and other Relevant Research Sources

(Fast-Track proposals will not be accepted.)

Evidence-based medicine should lead to clinicians and health care systems applying the best available data to the care of their patients-particularly data from publicly supported research and research from other peer reviewed sources. One major problem in achieving this goal is that neither physicians nor health care systems have any methods to assess the effectiveness and outcomes of evidence-based interventions. The purpose of this SBIR Phase I is to develop these model systems and data banks for mental health interventions. Since Phase I is to establish feasibility, the focus should be on establishing a model relevant to a particular disorder (major depressive disorders including bipolar disorder; schizophrenia; autism; Alzheimer's Disease etc) that takes into consideration human developmental factors, the full context of treatment factors and outcomes (symptoms, physical, social,

cognitive functioning), factors related to the service delivery system(as available) and relevant factors associated with gender, race, culture and co-morbidity. Attention should be given to transitional situations such as the transition to adulthood, the transition to assisted living or high levels of ADL/IADL care for the elderly, transitions into and out of different systems of care (foster care, correctional facilities, etc) since access to care/continuity of treatment is often affected by these transitions.

For example, for physicians to integrate evidence into everyday practice, they first must know the evidence from group (nomothetic) data and integrate this with individual (ideographic) data from patients. To "know the evidence" requires a system of dissemination of data from high-quality randomized clinical trials (effectiveness data) and other relevant research sources (e.g. epidemiologic data for rare side effects, services research) such as those supported by the NIMH that is available in a usable format. To integrate the evidence with the unique aspects of individual patients, physicians must conduct "N of 1" experiments. But without knowing the outcomes of the aggregate "N of 1" experiments, the overall effectiveness of evidence-based interventions will not be known for the larger group of patients with a full range of co-morbid conditions.

To be responsive to this request for contract an offer must propose: a)a plan for the dissemination of evidence based interventions to clinicians for a major mental disorder; b) outcomes of those interventions for their patients with this disorder; c) a feedback system for clinicians to assess the outcomes of the entire group of patients with this disorder in their healthcare system; and d) the implementation of equipoise randomization of competing interventions in routine clinical care of patients with this disorder to assess effectiveness; and e) a system of continuous clinical improvement for clinicians to use the results of randomized and nonrandomized outcome data from their own patients. The offeror should also include a plan for the recruitment of relevant stakeholders/end users from academic research centers, clinical practices, health care/mental health care practices and the public sector.

058 Families as Research and Treatment Partners: Developing Evidence Based Decision Aids for Mental Health Treatment Decisions

(Fast-Track proposals will not be accepted.)

Increasingly, families are being asked to participate in research and treatment related activities. However, there are very few scientifically based tools to assist family members in their choices and to facilitate their continued involvement in treatment/research. The purpose of this contract is to develop an array of decision aids including interactive educational and dissemination modules. Anticipated outcomes for Phase I include the development of draft: (1) evidenced based decision aids; (2) interactive educational materials; (3) evaluation/outcome criteria; and (3) protocols for the testing of these modules. Particular attention should be paid to developing appropriate materials and strategies to engage underserved minority and rural families in this process, to develop strategies and materials that are developmentally appropriate and to consider mental health treatment within a broad health and life-style context (e.g., implications of weight gain associated with certain medications). Critical times such as transitional phases (e.g., transition to adulthood, transition to assisted living in late life, transition between facilities such as schools, correctional, foster-care, emergency care) should be included since these are often the periods of greatest need and uncertainty for patients/families and the mental health care system.

Although this request is broad-based across ages, disorders and scientific paradigms, the following is illustrative. Attention Deficit Hyperactivity Disorder (ADHD) is one of the most commonly diagnosed psychiatric disorders of childhood and often persists into adolescence and adulthood. Providing quality of care for children, adolescents and adults with ADHD in the primary care setting has proved challenging. Efforts to implement the American Academy of Pediatrics (AAP) guidelines have revealed several barriers to providing evidence-based care, including lack of physician familiarity with the latest evidence on management issues and need for better family education and support. Viewed within the National Initiative for Children’s Healthcare Quality (NICHQ) Care Model for Child Health, the barriers identified demonstrate a clear need for decision support and self/family management support. Decision aids hold promise as a tool to address these areas of need. Decision aids are designed to provide tailored, evidence-based information on treatment options (that include all areas of cognitive, health and social functioning), including the likelihood of benefits and risks. In addition, they provide a mechanism to elicit patient and family preferences and values as they relate to the various treatment options. The goal is to empower an informed patient/family to share in

treatment (treatment research) to the degree that they are comfortable. In terms of the NICHQ Care Model, decision aids are designed to increase productive interactions between informed and activated patient/family and a prepared, proactive practice team. Ultimately, patient- and family-centered participation in the decision-making process may promote a partnership, where the family and the practice team pursue common goals and share confidence in the chosen treatment / research plan.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

IMMUNIZATION SAFETY OFFICE (ISO)

VACCINE TECHNOLOGY DEVELOPMENT TEAM (VAXDEV)

The Vaccine Technology Development (VAXDEV) team of the Immunization Safety Office (ISO) works on a variety of technological initiatives, projects, standards, and applied research which enhance the safety of immunization, promote improved systems and practices for monitoring vaccine safety, and otherwise promote the research, development, uptake and monitoring of new and safer vaccines (http://www.cdc.gov/nip/dev). A major priority is promoting safer, simpler, and swifter vaccine delivery technologies to overcome the dangers and drawbacks of using needle-syringe to administer vaccine.

001 Develop Methods to Enhance Administration of Vaccines, Including Live Virus Vaccines, Through the Respiratory Tract

Because of the drawbacks associated with injection of vaccines using syringes and needles, development of alternate methods of vaccine administration is a research priority. We are requesting proposals for methods to enhance the delivery of vaccines through the respiratory tract. Proposals should address: 1) Respiratory delivery methods for vaccines, including but not limited to aerosols, dry powders and nasal sprays; 2) Methods for improving the uptake or effectiveness of vaccines delivered through the respiratory tract; 3) Methods for evaluating deposition of vaccines in the respiratory tract, including but not limited to computer simulation models and in vitro models; or 4) Methods for facilitating study of vaccines delivered through the respiratory tract in animal models.

002 Disposable-Cartridge Jet Injector Technology

Prompt protection of public health in response to pandemic, local or regional epidemic, or bioterror threat may require rapid vaccination of a large proportion of the population with limited health personnel. High-speed, multi-use-nozzle jet injectors (MUNJIs) in which the same orifice and fluid pathway are used on consecutive vaccinees, have been used successfully with a variety of vaccines since the 1950s, but withdrawn from public health use in the 1990s after causing a hepatitis B outbreak and accumulating data suggesting they may transmit infectious bloodborne pathogens from one patient to the next. A new generation of disposable-cartridge jet injectors (DCJIs) that avoid this concern were introduced in the 1990s, but they generally are not designed for rapid use in mass vaccination campaigns. DCJIs also offer a means for developing countries to overcome the dangers and drawbacks of using needle-syringes, including unsterile re-use, needlestick injuries, and improper disposal.

Proposals are invited for disposable-cartridge jet injector technology for affordable use in both developed and developing countries for high-speed mass campaigns and/or slow-speed, routine immunization. Proposals may be for new or improved injectors, or for associated technology, such as filling systems or accessories, auto-reconstitution of lyophilized vaccines, and other related or useful components.

Proposals that promote standardization of cartridge-injector interfaces among different companies through appropriate licensing arrangements will be given priority consideration because of the public interest in universal standards for their cartridges, which should be designed for end-user filling of existing, off-the-shelf vaccines, as well as adaptable for vaccine manufacturer pre-filling in which the cartridge becomes the primary vaccine container.

NATIONAL CENTER FOR CHRONIC DISEASE PREVENTION AND HEALTH PROMOTION (NCCDPHP)

The NCCDPHP plans, directs, and coordinates programs in health promotion, chronic disease prevention, and reproductive health to enhance quality of life, improve reproductive health, and reduce the incidence of heart disease, stroke, cancer, diabetes, arthritis, obesity, oral disease, infant and maternal morbidity and mortality, unintended pregnancy, and emerging chronic

diseases. NCCDPHP uses two essential criteria to prioritize its research portfolio, societal burden and disproportionate burden. NCCDPHP places high priority on chronic diseases and conditions and reproductive health outcomes that have the greatest total impact on health, longevity, and quality of life. NCCDPHP places high priority on eliminating disproportionate burden related to sex, age, race, ethnicity, geography, sexual orientation, socioeconomic status, disability, and special needs. NCCDPHP supports three primary types of applied research, research on cause (determinant research), research on effect (intervention research), and research on application and benefit (dissemination research). NCCDPHP emphasizes cross-cutting research that is participatory, accounts for social and ecological factors, and is implemented at multiple levels.

NCCDPHP has identified ten priority research areas: 1) develop new measures and research designs to strengthen the quality of research; 2) identify the underlying determinants of racial and ethnic health disparities; 3) develop and evaluate interventions to eliminate health disparities; 4) examine established and emerging risk factors for chronic disease and investigate their potential for public health interventions; 5) assess the effectiveness of policy and environmental interventions to promote health; 6) improve the processes and outcomes of health care systems; 7) develop effective communication strategies to promote health; 8) examine methods for helping people manage their own health; 9) develop and evaluate the effectiveness of population-based health promotion and disease prevention policies and programs at the local, state, national, and international levels; 10) examine approaches for effectively translating successful community interventions into widespread practice. For examples of specific research questions in each of the ten priority areas, see *Setting the Agenda: CDC Research in Chronic Disease Prevention and Health Promotion*, available at http://www.cdc.gov.

This solicitation invites proposals in the following areas:

DIVISION OF ADULT AND COMMUNITY HEALTH (DACH), PREVENTION RESEARCH CENTERS PROGRAM

The Prevention Research Centers Program (www.cdc.gov/prc) enables CDC to fund extramural research centers that add to knowledge and practice of chronic disease prevention and control. It aims to:

1. Build partnerships that draw on the perspectives and resources of diverse communities and actively partner with them.
2. Build long-term relationships for engaging communities as partners in research.
3. Work with populations having the greatest burden of disease and disability, especially people affected by adverse socioeconomic conditions.
4. Implement and evaluate interventions that help improve health outcomes.
5. Strive to develop communities' long-term capacity.
6. Disseminate successful results to comparable communities throughout the nation.
7. Promote the quality and availability of public health services through proven interventions.
8. Train and offer technical assistance to community and public health practitioners.
9. Strengthen the public health infrastructure by sharing information, offering training and technical assistance, and testing interventions for implementation.
10. Facilitate communication among public health professionals and community members through conferences, training, publications, and other means.

NCCDPHP/DACH has identified one research area for which proposals are solicited:

025 Development and Evaluation of Eyewear for Citrus Workers

Eye injuries are among the most prevalent, costly, and disabling injuries in agricultural work and harvesting of citrus fruits is particularly hazardous because the workers are surrounded by a tree canopy. Eye injuries result from: penetrating and blunt trauma caused by brush, branches and plants; chemical burns from pesticides and solvents; infection, allergy, and irritation caused by foreign bodies from dust, debris, metal shards, and particulates; and cataracts and pterygium caused by exposure to the UV light of the sun. While data on occupational injuries among citrus workers has not been published, citrus company managers in Florida regularly report eye injuries as the most common ones experienced by their employees. Studies of serious occupational eye injuries have demonstrated that safety glasses would prevent the majority of injuries if used; however, worker acceptance is low,

primarily because current safety eyewear models are poorly suited for harvesting citrus in hot, humid conditions.

Since 2004, the Partnership for Citrus Worker Health (PCWH) together with the University of South Florida Prevention Research Center funded by CDC, has been conducting an intervention to promote safety glasses use among citrus pickers in Florida. Florida's nine billion dollar citrus industry depends on approximately 15,000 migrant farm workers, to harvest 748,000 acres of fruit by hand each year. Citrus harvesting is hot, dirty, backbreaking work. It takes place outdoors during some of the warmest months of the year. Citrus pickers work at their own pace, using a canvas bag and a ladder, to harvest an average of two to three tons of citrus per day. Because they are mainly paid by the piece-rate, they pick rapidly with little concern for safety.

Using trained eye safety promoters, the partnership has been able to increase use of safety glasses from zero to over 30%. In the first season of the project, the promoters tested approximately 20 different styles of glasses before deciding on the criteria that made for effective protective eyewear for citrus workers. Pilot tests revealed that safety glasses need to be lightweight and with frameless lenses to minimize distortion. The most appropriate lens color is a medium, indoor/outdoor tint to reduce sunlight but not hinder work in a shaded tree canopy. Other important features are: a soft rubber nose piece that elevates the lens of the glasses off the cheekbones of the face, a gap in the top of the glasses between the lens and the frame to vent heat from the face, and adjustable arms to adapt to a variety of facial sizes. Finally, a "sports style" band must be attached to the glasses that can keep them securely on the worker's head without the risk of entanglement in the branches.

While commercially available safety glasses have been used for three rounds of pilot-testing, workers report continued problems with their use that prevent widespread adoption. A qualified small business would be funded to develop and test appropriate, effective, and inexpensive safety eyewear for use in Florida's environment and potentially in other tree crop industries and locations.

In addition to the features mentioned above, glasses must be appropriate for harvesting citrus in the presence of extreme heat, humidity, and dust. Temperatures during harvest season often reach well into the 90's with humidity at 70%, making most safety glasses fog. As worker's sweat mixes with dirt and dust, the lenses get dirty and workers must take time to clean them. Another challenge is to design glasses so they can be used early in the morning when the trees are still wet and droplets from the dew fall on the lenses, obstructing pickers' vision as they stand on the high ladder. Finally, glasses must be inexpensive and either scratch resistant or designed so scratched lenses be replaced if they are scratched. CDC, USF Prevention Research Center and the PCWH are prepared to provide preliminary data on worker preferences, access to test populations, and researchers who can work with citrus harvesters to pilot test prototype eye wear.

OFFICE ON SMOKING AND HEALTH (OSH)

NCCDPHP/OSH has identified two research areas for which proposals are requested:

026 Linking GIS Technology with Essential Public Health Services

We predict that, by the year 2010, GIS applications in public health practice will no longer consist of the ad hoc approaches we have seen in the 1990s. By the year 2010, we expect to see GIS technology customized for public health applications. This GIS health software will offer applications that "know" which data systems are needed and where they are located. After loading the appropriate data and performing relevant analyses, the system will offer alternative courses of action ranging from informing other people in the public health system to issuing health advisories.

In what follows, we give several examples of the way public health practitioners are likely to routinely use GIS technology in the year 2010, organized according to the 10 consensus "essential public health services" identified in 1994 by US Public Health Service agencies and major national public health organizations.(29-31). CDC is currently pilot-testing performance standards for state and local public health systems based on this framework (for more details, see the National Public Health Performance Standards Program's website).

Tobacco-related example:

Inform, educate, and empower people about health issues. One of a community's identified priorities is to develop an **anti-smoking campaign**. An anti-smoking coalition uses GIS technology and commercial lifestyle segmentation profiles (or a public health analogue developed by CDC by 2010) **to identify subgroups** that are most likely to include active smokers, the Census blocks where active

smokers are most likely to reside, and the **most effective communication media and times of day** to deliver anti-smoking messages to these subgroups.

027 Tools to Enhance the Utilization of Tobacco Cessation Quitlines

The Office on Smoking and Health is submitting this call for proposals to have a small business collaborate with a quitline vendor, state health department, or other agency that supports or operates a tobacco cessation quitline to:

1) Develop tools that will educate the public and health care providers about the services that are provided to quitline callers. These educational tools could be produced in many different formats including but not limited to CD's, instructional videos, pamphlets, and web-based information. An assessment should be made on what format(s) will reach the largest number of potential quitline users and health care providers. Special emphasis should be given to developing tools that can be used to educate high risk or underserved populations.
2) Develop tools that will enhance referrals to tobacco cessation quitlines and the exchange of information to and from quitlines. These tools could be in many potential formats including but not limited to web-based interfaces, automatic messaging, and text messaging. An assessment should be made on format(s) that will achieve the largest increase in the number of patients referred and the number of patients ultimately counseled by the quitline.
3) Propose strategies for effective utilization of the tools among the public and practitioners.
4) Propose a plan for distribution of final product(s) to the public and to practitioners.

The significance of this proposed solicitation is that while tobacco cessation services are available in every state through the 1-800-Quit Now national portal number quitlines are underutilized. A significant barrier to the utilization of quitlines has been lack of knowledge about the specific services that will be provided to the tobacco user who calls the quitline. Additional information on what is provided through quitlines is also needed for health care providers who are a major source of referrals to quitlines. Also, referrals and the exchange of information both to and from the quitlines to health care providers need to be enhanced to maximize the number of referrals that quitlines are receiving. Development of these tools will increase the number of tobacco users who utilize effective tobacco cessation treatments in their quit attempts and will ultimately increase the numbers of successful quitters.

NATIONAL CENTER FOR HIV, STD AND TB PREVENTION (NCHSTP)

The mission of NCHSTP is to provide national leadership in preventing and controlling human immunodeficiency virus, other sexually transmitted diseases, and tuberculosis by working with community, state, national, and international partners in effective multi-disciplinary programs of surveillance, research, and evaluation.

This solicitation invites proposals in the following areas:

DIVISION OF AIDS, STD, AND TB LABORATORY RESEARCH

This contract proposal solicitation has been amended to include the following 5 topics.

019 Development of Novel Genotyping Procedures for Mycobacterium Tuberculosis

The Institute of Medicine Report identified the need for better methods for genotyping of M. tuberculosis strains to facilitate and focus tuberculosis control efforts. Currently available methods are too costly, time consuming, technically demanding, or labor intensive to be applicable at the local level. This contract seeks to develop field-expedient genotyping technology including clinical laboratory tests and accompanying instrumentation. The technology should be readily usable by staff in State and Local Public Health Laboratories. The following are particular areas of interest:

a) Development and evaluation of instrumentation to facilitate genotyping by the spoligotyping or MIRU typing methods in a cost-efficient manner.
b) Development and evaluation of new methods for genotyping M. tuberculosis strains.

020 New Laboratory Tests for Tuberculosis and Detection of Drug Resistance

In order to accomplish the Healthy People 2010 goal of reducing the time required for the laboratory confirmation of the diagnosis of tuberculosis to 48 hours, rapid tests to detect Mycobacterium tuberculosis or its products are needed. In addition,

rapid tests that can reduce the turnaround-time for detection of drug-resistance are needed. This contract seeks to develop field-expedient testing technology (including clinical laboratory tests and accompanying instrumentation) to detect M. tuberculosis or its products in patient specimens and/or to determine drug resistance of M. tuberculosis isolates. The technology should be readily usable by staff in clinical and public health laboratories. The following are particular areas of interest:

a) Development and evaluation of procedures and instrumentation to facilitate nucleic acid amplification testing methods for M. tuberculosis and optimize the ease-of-use and cost-efficiency of nucleic acid amplification testing.

b) Development of rapid cost-efficient methods to detect and identify Mycobacterium tuberculosis or its products in patient specimens suitable for use in clinical laboratories.

c) Development of rapid cost-efficient methods and accompanying instrumentation to determine drug resistance of M. tuberculosis isolates suitable for use in clinical laboratories.

DIVISION OF TUBERCULOSIS (TB) ELIMINATION (DTBE)

021 Development of a Novel Information System for Remote TB Control and Prevention Programs

As noted in CDC's response to the IOM TB report, goal one reflects activities related to maintaining control of TB. While remarkable advances have been accomplished on the US mainland, appropriate and effective infrastructure and TB information systems to support surveillance, reporting, and patient-centric interventions have been challenging to implement and maintain in the US-affiliated Pacific Island Jurisdictions (PIJ). The PIJs are very remotely situated from the US mainland and they grapple with tremendous geographical distances within jurisdictions creating an environment which does not readily support reliable information systems.

This contract seeks to develop an information system using established standards which will enable PIJs to overcome unique conditions such as (1) the varying protocols established by WHO and CDC; (2) the lack of data communication between rural and urban health centers; (3) the inadequate internet connectivity. Proposals should reflect systems development that incorporates both non-web based and web-based solutions. Sole web-based solutions are not realistic for this region.

- Development of a system which incorporates TB data collection standards from WHO DOTS, Secretariat of the Pacific Community, and CDC
- Development of a system to provide the ability to monitor and evaluate program processes and outcomes which are useful for surveillance, reporting, prevention and control activities to ensure that patient-centered case management and monitoring of treatment outcomes are the standard of care for all TB patients in the PIJs
- Development of a system which builds the capacity of PIJ TB control programs to conduct systematic and comprehensive reviews of TB patients
- Development of a system which improves and enhances TB laboratory capabilities
- Development of a system which must work on the current software capacity (MS Office) and/or limited dial-up Internet access
- Development of a system which captures necessary patient and laboratory information yet is optimized for querying large amounts of data to support program evaluation activities and CDC reporting and monitoring requirements
- Development of a system which supports access by multiple users across multiple PIJs to allow for national data collection
- Development of a system which utilizes technologies which can be supported locally
- Development of a system which addresses the challenges of intermittent Internet access.

NATIONAL CENTER ON BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES (NCBDDD)

NCBDDD provides national leadership for preventing birth defects and developmental disabilities and for improving the health and wellness of people with disabilities.

This solicitation invites proposals for the following topic area:

006 Generic Targeting of Thrombotic Risk

Overview/Significance: Bleeding complications from anticoagulation therapy are not only associated with significant morbidity and mortality but also has a considerable economic impact. Anticoagulation with warfarin is particularly problematic because correct dosing is complicated and is frequently inaccurate. Incorrect dosing which can lead to either over or under-coagulation can not only cause clinically significant bleeding but can also be fatal. Because individual responses to warfarin are different and dosing which must be established for each patient can change during therapy, frequent monitoring is essential. However determining the appropriate dose is empirical and difficult. The identification and clinical use of genetic targets which would allow for a more accurate determination of dosing will be significant.

Impact: The most commonly prescribed anticoagulant is warfarin and is the 11th over-all most prescribed drug in the U.S. Warfarin is used in the pharmacological management of thrombophilia (venous and arterial), atrial fibrillation, stroke, mechanical valve replacement and myocardial infarction. Because of the problems inherent in warfarin management, it is under-under utilized particularly with respect to stroke where it has been shown that 20 strokes can be prevented per one related bleeding episode. Defining better therapeutic benchmarks for individual dosing can not only prevent warfarin related bleeding complications but may also have significant impact in stroke prevention.

Objective: Luminex-based technology represents a platform that will allow for rapid analysis of both SNPs and proteins in a multiplex format. This format allows for the simultaneous measurements of multiple targets from a single well thus not only increasing throughput but also maximizing sample usage. This technology has the potential to be extremely useful in management of the thrombophilia patient and other patients who require anticoagulation. In terms of the individual thrombophilic patient, this approach not only can identify genetic risk factors for VTE but may also identify genetic factors which can be predicative for anticoagulation dosing (i.e. Warfarin). In addition this technology may also be used to measure multiple proteins (i.e. coagulation, inflammatory proteins) which may also be associated with thrombophilia. The identification of genetic polymorphisms that can affect warfarin dosing will have a huge population effect because individuals with stroke, atrial fibrillation, mechanical heart valves and acute myocardial infarction may also be anticoagulated with warfarin. Consequently the development of a multiplex SNP panel that consists of warfarin metabolism-related genes (i.e VKOR, cytochrome P450) that may or may not have additional SNPs for thrombotic risk has the potential to be a prevention tool. This undertaking will take advantage of an on-going DHBD study that is looking for new warfarin related SNPs in African-Americans.

Need: The development of a luminex based-multiplex panel with to be determined SNPS related to warfarin metabolism and thrombotic risk.

HUMAN SUBJECTS RESEARCH GUIDANCE AND INFORMATION SUPPLEMENT

PREPARING THE HUMAN SUBJECTS RESEARCH SECTION OF THE RESEARCH PLAN

In the Human Subjects Research section of the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets (1) the requirements of the HHS regulations to protect human subjects from research risks (45 C.F.R. Part 46), (2) the requirements of NIH policies for data and safety monitoring of clinical trials, and (3) the requirements of NIH policies on inclusion of women, minorities, and children. See Instructions Pertaining to Non-Exempt Human Subjects Research.

If the research is exempt from the requirements in the Federal regulations, you must provide a justification for the exemption with sufficient information about the involvement of the human subjects to allow a determination by peer reviewers and NIH staff that claimed exemption(s) is/are appropriate. See Exempt Human Subjects Research.

Applications must comply with this requirement; if not, application processing may be delayed or the application may be returned to the applicant without review.

For all research involving human subjects, a part of the peer review process will include careful consideration of protections from research risks, as well as the appropriate inclusion of women, minorities, and children. The Scientific Review Group (SRG) will assess the adequacy of safeguards of the rights and welfare of research participants, and the appropriate inclusion of women, minorities, and children, based on the information in the application.

To assist you in completing the Human Subjects Research portion of the Research Plan, we have provided six possible scenarios. All research will fall into one of these six scenarios. Determining which scenario best matches your proposed research depends on your answers to the following five questions:

Question 1: Does your proposed research involve human subjects?

Question 2: Does your proposed human subjects research meet the criteria for one or more of the exemptions in the HHS regulations (45 C.F.R. Part 46)?

Question 3: Does your proposed research meet the definition of clinical research?

Question 4: Does your proposed research include a Clinical Trial?

Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

Click on the questions and when you can answer the five questions, select the scenario that best matches your responses, and then follow the instructions provided for the scenario you choose.

HUMAN SUBJECTS RESEARCH

Question 1: Does your proposed research involve human subjects?

The first thing you must determine is whether or not your research involves human subjects, either at the applicant organization or at any other performance site or collaborating institution (e.g., subcontractors, consultants).

The research described in your application may include more than one research project; thus the application may include individual projects that meet the requirements for non-exempt or exempt human subjects research, or are not defined as human subjects research.

If research activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution, then your answer is "Yes" even if the research is exempt from regulations for the protection of human subjects.

The HHS regulations "Protection of Human Subjects" (45 C.F.R. 46, administered by OHRP) define a *human subject* as a living individual about whom an *investigator* conducting *research obtains*:

- data through *intervention* or *interaction* with the individual or
- *identifiable private information*

Investigator: The OHRP considers the term investigator to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. However, if the individuals who provide *coded* information or specimens also collaborate on other activities related to the conduct of the research with the investigators who receive such information or specimens, they will be considered to be involved in the conduct of the research. [OHRP's Coded Specimen Guidance]

Research: HHS regulations define *research* at 45 C.F.R. 46.102(d) as follows:
Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Obtains: In its guidance for use of coded specimens, OHRP has determined that under the definition of human subject at 45 C.F.R. 46.102(f), *obtaining* identifiable private information or identifiable specimens for research purposes constitutes human subjects research. *Obtaining* means receiving or accessing identifiable private information or identifiable specimens for research purposes. OHRP interprets *obtaining* to include an investigator's use, study, or analysis for research purposes of *identifiable private information* or identifiable specimens already in the possession of the investigator.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. (45 C.F.R. 46.102(f))

Interaction includes communication or interpersonal contact between investigator and subject. (45 C.F.R. 46.102(f))

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record). Private information must be *individually identifiable* (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. (45 C.F.R. 46.102(f))

Individually Identifiable Private Information: According to its guidance for use of coded specimens, OHRP generally considers private information or specimens to be *individually identifiable* as defined at 45 C.F.R. 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through *coding* systems. Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research Using Human Specimens or Data:

Regulatory requirements (Federal and state) to protect human subjects apply to a much broader range of research than many investigators realize, and researchers using *human specimens and/or data* are often unsure about how regulations apply to their research. Regulatory obligations to protect human subjects would apply, for example, to research that uses –

- Bodily materials, such as cells, blood or urine, tissues, organs, hair or nail clippings, from living individuals who are individually identifiable to the investigator(s), even if these materials were collected by others;
- Residual diagnostic specimens from living individuals that are individually identifiable to the investigator(s), including specimens obtained for routine patient care that would have been discarded if not used for research;
- Private information, such as medical information, about living individuals that is individually identifiable to the investigator(s), even if the information was not specifically collected for the study in question. This includes research on genetic information that can be readily associated by the investigator(s) with identifiable living individuals.

The definition of "human subject" includes, but is not limited to, human organs, tissues, and body fluids from living individuals, as well as private graphic, written, or recorded information about living individuals, if (1) there is interaction or intervention with a living individual to obtain the specimens or data for research purposes, or (2) the identity of the subjects can be readily ascertained by the investigator or other members of the research team.

Research that involves only *coded* private information/data or coded human biological specimens may not constitute human subjects research under the HHS human subjects regulations (45 C.F.R. Part 46) if:

- the specimens and/or private information were not collected specifically for the currently proposed research project through an interaction/intervention with living individuals AND
- the investigator(s) (including collaborators) on the proposed research cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain (e.g., the researcher's access to subject identities is prohibited by written repository procedures and policies and/or through an agreement signed between the recipient researcher and the repository providing the specimens and/or data). [See definitions below and the following guidance from the Office for Human Research Protections (OHRP) for additional information and examples: http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf.]

Individuals who provide *coded* information or specimens for proposed research and who also collaborate on the research involving such information or specimens are considered to be involved in the conduct of human subjects research.

Coded: With respect to private information or human biological specimens, *coded* means that:

(1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol or combination thereof (i.e., the code); and

(2) a key to decipher the code exists, enabling linkage of the identifying information with the private information or specimens.

You may find it helpful to consult the following guidance from OHRP:

- OHRP Decision Charts: http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm
- OHRP Policy on Coded Specimens and Data: http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf
- OHRP Guidance on Repositories: http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm; http://www.hhs.gov/ohrp/humansubjects/guidance/guid1223.pdf

With regard to the engagement of performance sites in proposed human subjects research, you may find it helpful to consult the following:

- OHRP Memo on Engagement: http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm

The decisions about when research involving human specimens and/or data from subjects is considered human subjects research are complex. The OHRP recommends that institutions have policies in place that designate the individual or entity authorized to determine whether proposed research is exempt from regulatory requirements to protect human subjects and that determinations should be made by someone other than the investigator.

You need to be aware that the involvement of human subjects in non-exempt research must be approved by your IRB prior to award.

The NIH Office of Extramural Research Human Subjects website contains additional information and Frequently Asked Questions that may help investigators understand how these regulations and Guidance documents apply to their research. See http://grants.nih.gov/grants/policy/hs/index.htm.

How can you determine whether research that involves only the use of specimens and/or data from pathology archives or a specimen bank and/or data repository is human subjects research?

The research described in your application may include more than one research project; thus the application may include separate projects that meet the requirements for either human subjects research, exempt human subjects research, or are not defined as human subjects research. Examples are provided below:

- If the specimens and/or data were obtained specifically for the currently proposed research project through intervention or interaction with a living individual, then your research is human subjects research.
- If you receive or have access to individually identifiable specimens or data from living individuals (e.g., pathology or medical records), your proposed research is human subjects research.
- If you receive or have access to existing individually identifiable private information or identifiable specimens from living individuals (e.g., pathology or medical records), but you as the investigator or your collaborator record the information in such a manner that you cannot subsequently access or obtain direct or indirect identifiers that are linked to the subjects the research project that you conduct using data recorded in this manner meets the requirements of Exemption 4. If you will retain or can access any identifiers, the research project is not exempt under Exemption 4.
- If you are using specimens and/or data and neither you nor your collaborators can identify the subjects from whom the specimens and/or data were obtained either directly or indirectly through coding systems, the HHS human subjects regulations (45 C.F.R. Part 46) do not apply at all.
- If your research involves only coded private information/data or coded specimens, OHRP does not consider this research to involve human subjects as defined under the HHS Protection of Human Subjects Regulations (45 C.F.R. Part 46.102(f)) *if* the following conditions are *both* met:
    - the private information/data or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; *and*
    - the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:

(a) the key to decipher the code is destroyed before the research begins;

(b) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased;

(c) there are IRB approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; ***or***

(d) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

What is not human subjects research under HHS regulations at 45 C.F.R. Part 46?

- Research that does not involve intervention or interaction with living individuals, or identifiable private information is not human subjects research (see definitions),
- Research that only proposes the use of cadaver specimens is not human subjects research, because human subjects are defined as "living individuals." The use of cadaver specimens is not regulated by 45 C.F.R. Part 46, but may be governed by other federal, state and local laws.

Guidance and Additional Instructions

If you answered "No" to Question 1, then proceed to Scenario A.

If you answered "Yes" to Question 1, then you may need to determine whether your research meets the criteria for an exemption from the Human Subjects Protection requirements. Proceed to Question 2.

If you need to consider an alternative scenario, return to the Decision Table.

EXEMPT HUMAN SUBJECTS RESEARCH

Question 2: Does your proposed human subjects research meet the criteria for one or more of the exemptions in the HHS regulations (45 C.F.R. 46)?

Some human subjects research is exempt from the HHS regulations (45 C.F.R. 46). OHRP guidance states that Exemptions should be independently determined (http://www.hhs.gov/ohrp/humansubjects/guidance/irb71102.pdf). Institutions often designate their IRB to make this determination. Because NIH does not require IRB approval at time of application, the exemptions designated in item 4a often represent the opinion of the PI, and the justification provided for the exemption by the PI is evaluated during peer review.

The research described in your application may include more than one research project; thus the application may include individual projects that meet the requirements for non-exempt or exempt human subjects research, or are not defined as human subjects research.

If research activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution, then your answer is "Yes" to Question 1 "Does your proposed research involve human subjects" even if the research is exempt from regulations for the protection of human subjects.

Research involving individuals who are or who become prisoners cannot be exempt under any exemption categories (see 45 CRF Part 46, Subpart C).

Your human subjects research is exempt if all of the proposed research meets the criteria for one or more of the following six exemptions.

Exemption 1: Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Exemption 2: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless:

(i) information obtained is recorded in such a manner that human subjects can be identified directly or through identifiers linked to the subjects and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

Exemption 2 for research involving survey or interview procedures or observation of public behavior, does not apply to research with children (see 45 C.F.R. Part 46, Subpart D), except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Exemption 3: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

Exemption 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

The humans subjects regulations decision charts (http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm) from the Office of Human Research Protection (OHRP) will help you to see whether your research falls under the human subjects regulations and if so, whether it meets the criteria for Exemption 4. See also the information contained at: Exemption 4 Guidance and Information.

The NIH Office of Extramural Research website also contains information that is helpful for determining whether your human subjects research meets the criteria for Exemption 4. See http://grants.nih.gov/grants/policy/hs/index.htm.

Research that meets the criteria for Exemption 4 is not considered "clinical research" as defined by NIH. Therefore the NIH policies for inclusion of women, minorities and children in clinical research do not apply to research projects covered by Exemption 4.

Exemption 5: Research and demonstration projects that are conducted by or subject to the approval of Department or Agency heads and that are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs (ii) procedures for obtaining benefits or services under those programs (iii) possible changes in or alternatives to those programs or procedures or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

Exemption 6: Taste and food quality evaluation and consumer acceptance studies (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Guidance and Additional Instructions

If you answered "Yes" to Question 2, then your research meets the criteria for an exemption.

- If your research meets the criteria for Exemption 4, then follow the instructions for Scenario B and read the information contained in Exemption 4 Guidance and Information.
- If your research meets the criteria for any of the other five exemptions, follow the instructions for Scenario C.

Remember that you need to identify which exemption(s) you believe is applicable to your research, and provide a justification for the exemption(s) with sufficient information about the involvement of human subjects to allow a determination by peer reviewers and NIH staff that the claimed exemption(s) is appropriate.

If you answered "No" to Question 2, then your research does not qualify for one of the exemptions, and your research is not exempt from full IRB review. Proceed to Question 3.

If you need to consider an alternative scenario, return to the Decision Table.

CLINICAL RESEARCH

Question 3: Does your proposed research meet the definition of clinical research?

The NIH defines Clinical Research as:

(1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies.

(2) Epidemiologic and behavioral studies.

(3) Outcomes research and health services research.

Clinical research that does not meet the criteria for a clinical trial or an NIH-defined Phase III clinical trial must follow the instructions in Scenario D.

Research projects that meet the criteria for Exemption 4 are not considered "clinical research." Investigators who propose research that meets the criteria for Exemption 4 must follow the instructions provided in Scenario B.

Guidance and Additional Instructions

If you answered "Yes" to Question 3, then proceed to Question 4 and Question 5 to determine whether your research meets the criteria for a clinical trial or an NIH-defined Phase III clinical trial.

If you answered "No," then you need to consider an alternative scenario. Return to the Decision Table.

CLINICAL TRIAL

Question 4: Does your proposed research include a clinical trial?

The NIH defines a *clinical trial* as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.

Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits these criteria of a clinical trial.

Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision-making for the subject or the test itself imposes more than minimal risk for subjects.

Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

Phase I clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range, and to identify side effects).

Phase II clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.

Phase III studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

Phase IV studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

Guidance and Additional Instructions

If you answered “Yes” to Question 4, then you will need to provide a general description of a Data and Safety Monitoring Plan. See Scenario E.

Also continue to Question 5 to determine whether your research meets the criteria for an NIH-defined Phase III clinical trial.

If you answered “Yes” to Question 3 (Clinical Research) and “No” to Question 4 (Clinical Trial), then follow the instructions for Scenario D.

If you answered “No” to Question 4, you will need to consider an alternative scenario. Return to the Decision Table.

NIH-DEFINED PHASE III CLINICAL TRIAL

Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

An *NIH-Defined Phase III Clinical Trial* is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of either evaluating an experimental intervention in comparison with a standard or control intervention or of comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

If your research meets the above criteria, then in addition to providing a Data and Safety Monitoring Plan, you will be expected to address whether you expect to find clinically important sex/gender and/or race/ethnicity differences in the intervention effect. The discussion may include supporting evidence and/or data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology, and other relevant studies.

You will be expected to provide a research plan that must include one of the following plans:

- Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, OR
- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender and racial/ethnic groups is not required as subject selection criteria, but inclusion is encouraged.), OR
- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups.

Guidance and Additional Instructions

If you answered “Yes” to Question 5, then follow the instructions for Scenario F.

If you answered “No,” then you need to consider an alternative scenario. Return to the Decision Table.

EXEMPTION 4 GUIDANCE AND INFORMATION

Research that meets the criteria for Exemption 4 is Human Subjects Research but it is not considered clinical research.

Exemption 4 includes research projects involving the collection or study of *existing* data, documents, records, pathological specimens, or diagnostic specimens, if these sources are *publicly available* or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through *identifiers* linked to the subjects.

What is meant by "existing" data or specimens?

Exemption 4 applies to retrospective studies of specimens and/or data that have already been collected. The materials must be "on the shelf" (or in the freezer) at the time the protocol is submitted to the IRB or other designated officials at your institution to determine whether the research is indeed exempt. Research that involves the ongoing collection of specimens and/or data does not meet the criteria for Exemption 4.

What is meant by "publicly available sources"?

This language in the regulation was intended to apply to public sources of data, such as census data. Its meaning with respect to human tissue specimens is widely debated. Although there are organizations that make human cells and tissues broadly accessible to the research community, these materials are not usually available to the public at large and are not generally considered to be publicly available.

What is meant by "identifiers linked to the subjects"?

Identifiers, such as names, social security numbers, medical record numbers, or pathology accession numbers, or other codes that permit specimens to be linked to living individuals and perhaps also to associated medical information.

How can I determine whether my research meets the criteria for Exemption 4?

The humans subjects regulations decision charts (http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm) from the Office of Human Research Protection (OHRP) will help you to see whether your research falls under the human subjects regulations and if so, whether a research project meets the criteria for Exemption 4.

OHRP advises that investigators should not have the authority to make an independent determination that research involving human subjects is exempt. OHRP guidance states that Exemptions should be independently determined (http://www.hhs.gov/ohrp/humansubjects/guidance/irb71102.pdf). Institutions often designate their IRB to make this determination. Because NIH does not require IRB approval at time of application, the exemptions designated in item 4a often represent the opinion of the Principal Investigator, and the justification(s) provided by the Principal Investigator for the exemption(s) is/are evaluated during peer review.

Information is also available on the NIH Office of Extramural Research website at http://grants.nih.gov/grants/policy/hs/index.htm.

How can you determine whether research that involves only the use of specimens and/or data from pathology archives or a specimen bank and/or data repository is human subjects research?

The research described in your application may include more than one research project; thus the application may include separate projects that meet the requirements for either human subjects research, exempt human subjects research, or are not defined as human subjects research. Examples are provided below:

- If the specimens and/or data were obtained specifically for the currently proposed research project through intervention or interaction with a living individual, then your research is human subjects research.
- If you receive or have access to individually identifiable specimens or data from living individuals (e.g., pathology or medical records), your proposed research is human subjects research.
- If you receive or have access to existing individually identifiable private information or identifiable specimens from living individuals (e.g., pathology or medical records), but you as the investigator or your collaborator record the information in such a manner that you cannot subsequently access or obtain direct or indirect identifiers that are linked to the subjects the research project that you conduct using data recorded in this manner meets the requirements of Exemption 4. If you will retain or can access any identifiers, the research project is not exempt under Exemption 4.
- If you are using specimens and/or data and neither you nor your collaborators can identify the subjects from whom the specimens and/or data were obtained either directly or indirectly through coding systems, the HHS human subjects regulations (45 C.F.R. Part 46) do not apply at all.
- If your research involves only coded private information/data or coded specimens, OHRP does not consider this research to involve human subjects as defined under the HHS Protection of Human Subjects Regulations (45 C.F.R. Part 46.102(f)) *if* the following conditions are *both* met:
    - the private information/data or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; *and*
    - the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
        (a) the key to decipher the code is destroyed before the research begins;
        (b) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased;
        (c) there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; *or*
        (d) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

Guidance and Additional Instructions

If your research meets the criteria for Exemption 4, refer to Scenario B.

If you need to consider an alternative scenario, return to the Decision Table.

INSTRUCTIONS PERTAINING TO NON-EXEMPT HUMAN SUBJECTS RESEARCH

In your application narrative, create a section entitled “E. Human Subjects Research” immediately following the last entry in the Research Design and Methods section. Although no specific page limitation applies to this section of the application, be succinct. Scientific Review Groups will assess each application as being “acceptable” or “unacceptable” with regard to the protection of human subjects.

As the first entry, create a heading entitled “Protection of Human Subjects.” Use subheadings to address the issues listed under items 1-4 below.

If your research includes a clinical trial, address item 5. "Data and Safety Monitoring Plan."

Protection of Human Subjects

1. RISKS TO THE SUBJECTS

a. ***Human Subjects Involvement and Characteristics***

- Describe the proposed involvement of human subjects in the work outlined in the Research Design and Methods section.
- Describe the characteristics of the subject population, including their anticipated number, age range, and health status.
- Identify the criteria for inclusion or exclusion of any subpopulation.
- Explain the rationale for the involvement of special classes of subjects, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.
- List any collaborating sites where human subjects research will be performed, and describe the role of those sites in performing the proposed research.

b. ***Sources of Materials***

- Describe the research material obtained from living human subjects in the form of specimens, records, or data.
- Describe any data that will be recorded on the human subjects involved in the project.
- Describe the linkages to subjects, and indicate who will have access to subject identities.
- Provide information about how the specimens, records, or data are collected and whether material or data will be collected specifically for your proposed research project.

c. ***Potential Risks***

- Describe the potential risks to subjects (physical, psychological, social, legal, or other), and assess their likelihood and seriousness to the subjects.
- Where appropriate, describe alternative treatments and procedures, including the risks and benefits of the alternative treatments and procedures to participants in the proposed research.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. ***Recruitment and Informed Consent***

- Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.

- Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. Informed consent document(s) need not be submitted to the PHS agencies unless requested.

b. ***Protection Against Risk***

- Describe planned procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assess their likely effectiveness.

- Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a description of the plan for data and safety monitoring of the research and adverse event reporting to ensure the safety of subjects.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

- Discuss the potential benefits of the research to the subjects and others.

- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.

- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

NOTE: Test articles (investigational new drugs, devices, or biologicals) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the Food and Drug Administration, and/or the status of requests for an IND or IDE covering the proposed use of the test article in the research plan.

5. DATA AND SAFETY MONITORING PLAN

- If your research includes a clinical trial, create a section heading entitled "Data and Safety Monitoring Plan."

- Provide a general description of a monitoring plan that you plan to establish as the overall framework for data and safety monitoring. Describe the entity that will be responsible for monitoring and the process by which Adverse Events (AEs) will be reported to the Institutional Review Board (IRB), the funding I/C, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration (FDA) in accordance with Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations. Be succinct. Contact the FDA (http://www.fda.gov) and also see the following websites for more information related to IND and IDE requirements:

http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr312_01.html (IND)
http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr812_01.html (IDE)

- The frequency of monitoring will depend on potential risks, complexity, and the nature of the trial; therefore, a number of options for monitoring trials are available. These can include, but are not limited to, monitoring by a:

  a. Principal Investigator (required)

  b. Independent individual/Safety Officer

  c. Designated medical monitor

  d. Internal Committee or Board with explicit guidelines

  e. Data and Safety Monitoring Board (DSMB). NIH specifically requires the establishment of ***Data and Safety Monitoring Boards*** (DSMBs) for ***multi-site*** clinical trials involving interventions that entail potential ***risk*** to the participants, and generally for Phase III clinical trials. Although Phase I and Phase II clinical trials may also use DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate.

  f. Institutional Review Board (IRB - required)

- A detailed Data and Safety Monitoring Plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). For additional guidance on creating this Plan, see the above reference.

Guidance and Additional Instructions

Proceed to Inclusion of Women and Minorities.

INCLUSION OF WOMEN AND MINORITIES

Create a section heading entitled "Inclusion of Women and Minorities" and place it immediately following the “Protection of Human Subjects” section. Although no specific page limitation applies to this section of the application, be succinct.

Scientific Review Groups will assess each application as being “acceptable” or “unacceptable” with regard to the protection of human subjects.

In this section of the Research Plan, address, at a minimum, the following four points:

1. The targeted/planned distribution of subjects by sex/gender and racial/ethnic groups for each proposed study or protocol using the format in the Targeted/Planned Enrollment Table. (Instructions for completing this table are provided below.) If you are using existing specimens and/or data that does not meet the criteria for Exemption 4 and you do not have access to information on the distribution of women and minorities, so state and explain the impact on the goals of the research as part of the rationale that inclusion is inappropriate (item 3 below). Alternatively, you may describe the women and minority composition of the population base from whom the specimens and/or data will be obtained. Include the Targeted/Planned Enrollment Table (MS Word or PDF) in this section.
2. A description of the subject selection criteria and rationale for selection of sex/gender and racial/ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study.
3. A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group (see examples below).
4. A description of proposed outreach programs for recruiting sex/gender and racial/ethnic group members as subjects.

Examples of acceptable justifications for exclusion of:

A. ***One gender:***

1. One gender is excluded from the study because:

- inclusion of these individuals would be inappropriate with respect to their health;
- the research question addressed is relevant to only one gender;
- evidence from prior research strongly demonstrates no difference between genders;
- sufficient data already exist with regard to the outcome of comparable studies in the excluded gender, and duplication is not needed in this study.

2. One gender is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects by gender (e.g., uniquely valuable stored specimens or existing datasets are single gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens).
3. Gender representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete gender documentation are used), and this does not compromise the scientific objectives of the research.

B. ***Minority groups or subgroups:***

1. Some or all minority groups or subgroups are excluded from the study because:

- Inclusion of these individuals would be inappropriate with respect to their health;
- The research question addressed is relevant to only one racial or ethnic group;

- Evidence from prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables;
- A single minority group study is proposed to fill a research gap;
- Sufficient data already exists with regard to the outcome of comparable studies in the excluded racial or ethnic groups and duplication is not needed in this study.

2. Some minority groups or subgroups are excluded or poorly represented because the geographical location of the study has only limited numbers of these minority groups who would be eligible for the study, and the investigator has satisfactorily addressed this issue in terms of:

- The size of the study;
- The relevant characteristics of the disease, disorder or condition;
- The feasibility of making a collaboration or consortium or other arrangements to include representation.

3. Some minority groups or subgroups are excluded or poorly represented because the purpose of the research constrains the applicant's selection of study subjects by race or ethnicity (e.g., uniquely valuable cohorts, stored specimens or existing datasets are of limited minority representation, very small numbers of subjects are involved, or overriding factors dictate selection of subjects, such as matching of transplant recipients or availability of rare surgical specimens).
4. Racial or ethnic origin of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or data sets with incomplete racial or ethnic documentation are used) and this does not compromise the scientific objectives of the research.

Additional Instructions and Requirements When NIH-Defined Phase III Clinical Trials Are Proposed

If your proposed research includes an NIH-Defined Phase III Clinical Trial, the section on Inclusion of Women and Minorities also must address whether you expect to find clinically important sex/gender and/or race/ethnicity differences in the intervention effect. The discussion may include supporting evidence and/or data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies. Your discussion of expected sex/gender and/or race/ethnicity differences in intervention effect must include selection and discussion of one of the following analysis plans:

- Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, *or*
- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender and racial/ethnic groups is not required as subject selection criteria, but inclusion is encouraged.), *or*
- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups.

Instructions for Completing the Targeted/Planned Enrollment Tables for Reporting Race and Ethnicity Data for Subjects in Clinical Research

A. New Applications and Clinical Research Studies begun after January 10, 2002:

All new clinical research studies should collect and report information on participants with respect to two categories of ethnicity and five categories of race. The new Inclusion Enrollment Report Table (MS Word or PDF) for reporting summary data on participants to NIH includes two categories of ethnicity and five categories of race and is based on recent changes by the Office of Management and Budget (OMB) regarding standards for data on race and ethnicity. Investigators should review the instructions and Frequently Asked Questions about using the new Enrollment Table format at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html.

When reporting these data in the aggregate, investigators should report: (a) the number of respondents in each ethnic category; (b) the number of respondents who selected only one category for each of the five racial categories; (c) the total number of respondents who selected multiple racial categories reported as the "number selecting more than one race," and (d) the number of respondents in each racial category who are Hispanic or Latino. Investigators may provide the detailed distributions, including all possible combinations, of multiple responses to the racial designations as additional information. However, more detailed items should be designed in a way that they can be aggregated into the required categories for reporting purposes.

For new applications and clinical research studies begun after January 10, 2002, use the Targeted/Planned Enrollment Table format (MS Word or PDF).

Provide the study title.

The '"Total Planned Enrollment" means the number of subjects that are expected to be enrolled during the entire period of the study and are needed to evaluate the research question The "Total Planned Enrollment" will be reported in two ways in the table: by "Ethnic Category" and by "Racial Categories."

"Ethnic Category": Provide the numeric distribution of the Total Planned Enrollment according to ethnicity and sex/gender in the top part of the table.

"Racial Categories": Provide the numeric distribution of the Total Planned Enrollment, this time by racial categories and sex/gender, in the bottom part of the table. Note that Hispanic is not a racial category.

If there is more than one study/protocol, provide a separate table for each.

List any proposed racial/ethnic subpopulations below the table.

How should I report race and ethnicity data when my research involves a foreign population?

Investigators are encouraged to design their data collection instruments in ways that allow respondent self-identification of their racial and ethnic affiliation. However, these items should be designed in a way that they can be aggregated into the required categories. Also, the investigator can report on any racial/ethnic subpopulations by listing this information in an attachment to the required table. This may be particularly useful when distinctive subpopulations are relevant to the scientific hypotheses being studied.

When completing the tables, investigators should asterisk and footnote the table indicating that data includes foreign participants. If the aggregated data only includes foreign participants, the investigator should provide information in one table with an asterisk and footnote. However, if the study includes both domestic and foreign participants, the investigator should complete two separate tables – one for domestic data and one for foreign data, with an asterisk and footnote accompanying the table with foreign data.

B. Clinical Research Studies begun before January 10, 2002:

If the proposed research uses existing data, then use the formats below for competing continuations and competing supplements. Investigators should review the instructions and Frequently Asked Questions about using the new Enrollment Table format at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html.

Competing Continuations:

For competing continuations involving the collection of new/additional clinical data, use the "Targeted/Planned Enrollment Table (MS Word or PDF)" and the instructions above. *Note:* If you choose to report information with the new Targeted/Planned Enrollment Table, you must continue to use this format for the remaining years of the project.

For competing continuations involving studies begun before January 10, 2002 that do not involve the collection of new/additional clinical data, the data on ethnicity/race and sex/gender may be presented in EITHER the Targeted/Planned Enrollment Table (MS Word or PDF) OR the 4/98 Version of the Inclusion Table (MS Word or PDF). If data were originally collected from study subjects using two questions (one about ethnicity and one about race) and subjects were given the option of selecting more than one race, then use the Targeted/Planned Enrollment Table. Otherwise, use the 4/98 Version of the Inclusion Table, which uses a combined race/ethnicity format with five categories.

Competing Supplements:

For competing supplemental applications involving studies begun before January 10, 2002, investigators may report ethnicity/race and sex/gender composition using EITHER the Inclusion Enrollment Report (MS Word or PDF) OR the 4/98 Version of the Inclusion Table (MS Word or PDF). If data are being collected using two questions (one about ethnicity and one about race) and subjects were given the option of selecting more than one race, then use the Targeted/Planned Enrollment Table. *Note:* If you choose to report information with the new Targeted/Planned Enrollment Table, you must continue to use this format for the remaining years of the project.

If data are being collected using one question that combines ethnicity and race, use the 4/98 Version of the Inclusion Table. For previously funded studies that used the 4/98 Version of the Inclusion Table the earlier reporting format is NOT directly transferable to the format.

C. What Inclusion/Enrollment Table Should Principal Investigators Use for Reporting Accrual Data to NIH? (New versus Old Table)

The following instructions apply to progress reports, whether submitted as part of a non-competing or competing application.

Guidelines for choosing the new Inclusion Enrollment Report Table versus the old Inclusion Table are as follows:

New Inclusion Enrollment Report (MS Word or PDF)

- Studies begun after January 10, 2002, must be designed to ask participants two questions, one about their ethnicity and one about their race, and investigators must use the new Inclusion Enrollment Report table format for reporting summary data to NIH.
- Principal investigators who started a study prior to January 10, 2002 using the old Inclusion Table format for reporting summary data to NIH may switch to the new Inclusion Enrollment Report format if they choose to do so, but they must also change their data collection methods to ask two questions (one about ethnicity and another about race) rather than one question (that combined race and ethnicity) for all participants enrolled in the study from that point on.
- For studies that began prior to January 10, 2002: When the study is submitted for competing continuation and plans to collect new/additional data, the principal investigator is required to change to the new standards for collecting data and use the new Inclusion Enrollment Report format for reporting data to NIH. In some cases, this will mean that principal investigators will need to re-ask study participants about

their race and ethnicity using the new two-question format. Note: principal investigators should not ask again about race and ethnicity if the subjects are no longer participating in the study.

Old Inclusion Table (4/98 Version) MS Word or PDF

- Studies begun prior to January 10, 2002 (and now in their non-competing Type 5 period) that were structured with one question about race and ethnicity may continue to report enrollment/accrual data to NIH based on the old form, i.e., using five categories of race/ethnicity. However, when they come in for competitive renewal, they will need to change to the new standards/new form for any additional data collection.
- Principal investigators should not switch to the new form if only one question about race and ethnicity is used in data collection.
- Sample of old Inclusion Table format: http://grants.nih.gov/grants/funding/women_min/InclusionOld_Form.pdf

Investigators who have questions about these choices should contact NIH program staff for advice.

Guidance and Additional Instructions

After you have completed the Inclusion of Women and Minorities section, proceed to Inclusion of Children.

INCLUSION OF CHILDREN

- Create a section entitled “Inclusion of Children” and place it immediately following the last entry in the Inclusion of Women and Minorities section.
- For the purpose of implementing these guidelines, a ***child*** is defined as an individual under the age of 21 years (for additional information see http://grants.nih.gov/grants/funding/children/children.htm and http://grants.nih.gov/grants/guide/notice-files/not98-024.html).
- Provide either a description of the plans to include children or, if children will be excluded from the proposed research, application, or proposal, then you must present an acceptable justification (see below) for the exclusion.
- If children are included, the description of the plan should include a rationale for selecting a specific age range of children. The plan also must include a description of the expertise of the investigative team for dealing with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.
- Scientific Review Groups will assess each application as being "acceptable" or "unacceptable" with regard to the age-appropriate inclusion or exclusion of children in the research project.
- When children are involved in research, the Additional Protections for Children Involved as Subjects in Research (45 C.F.R. 46 Subpart D) apply and must be addressed in the “Human Subjects Research and Protection from Risks” subheading.

Justifications for Exclusion of Children

For the purposes of this policy, all individuals under 21 are considered children; however, exclusion of any specific age group, such as individuals under 18, should be justified in this section.

It is expected that children will be included in all clinical research unless one or more of the following exclusionary circumstances can be fully justified:

1. The research topic to be studied is not relevant to children.
2. There are laws or regulations barring the inclusion of children in the research.
3. The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be needlessly redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.
4. A separate, age-specific study in children is warranted and preferable. Examples include:
   a. The condition is relatively rare in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition); or
   b. The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
   c. Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages or different age-related metabolic processes). While this situation may represent a justification for excluding children in some instances, consideration should be given to taking these differences into account in the study design and

expanding the hypotheses tested, or the interventions planned, to allow inclusion of children rather than excluding them.

5. Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). Although children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.
6. Study designs are aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children).
7. Other special cases can be justified by the investigator and found acceptable to the review group and the Institute Director.

Guidance and Additional Instructions

See Policy on Inclusion of Children.

SCENARIO A: NO HUMAN SUBJECTS RESEARCH PROPOSED

Criterion:

If you are uncertain as to whether your research involves Human Subjects please read: Question 1: Does your proposed research involve human subjects?

Instructions:

Check the box marked “No” on the Face Page (item 4).

In your application narrative, create a heading labeled “E. Human Subjects Research” and place it immediately after the last entry in the Research Design and Methods section. Include the following statement below the heading: “No Human Subjects Research is proposed in this application.”

If your proposed research involves human specimens and/or data from subjects, please provide a justification for your claim that no human subjects are involved (see guidance under Question 1: Does your proposed research involves human subjects?).

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

Do not follow the instructions for Scenario A if research activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution. You will need to consider an alternative scenario.

If you need to consider an alternative scenario return to the Decision Table.

SCENARIO B: HUMAN SUBJECTS RESEARCH CLAIMING EXEMPTION 4

Criteria:

Human Subjects Research	Yes
Exemption	4
Clinical Research	No
Clinical Trial	N/A
NIH-Defined Phase III Clinical Trial	N/A

Instructions and Required Information:

Although no specific page limitation applies to this section of the application, be succinct in your responses.

Check the box marked “Yes” on the Face Page (item 4). Check “’Yes” if activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution. “Yes” should be checked even if the research is exempt from requirements in the Federal regulations for the protection of human subjects (45 C.F.R. 46).

Indicate that you are claiming Exemption 4 on the Face Page (item 4a) and enter “NA” for item 4b, since no assurance is needed.

In your application narrative, create a heading entitled “E. Human Subjects Research” and place it immediately after the last entry in the Research Design and Methods section. Include the following statement below the heading: “This Human Subjects Research falls under Exemption 4.”

Address the following three items in this new section:

1. Human Subjects Involvement and Characteristics:

a. Describe the proposed involvement of human subjects in the work outlined in the Research Design and Methods section.

b. Describe the characteristics of the subject population, including their anticipated number, age range, and health status. If the characteristics of the population are not available, then the applicant should indicate that the information is unknown.

c. Identify the criteria for inclusion or exclusion of any subpopulation.

d. Explain the rationale for the involvement of vulnerable populations, such as fetuses, neonates, pregnant women, children, institutionalized individuals, or others who may be considered vulnerable populations. Exemptions 1-6 do not apply to research involving prisoners or subjects who become prisoners (see 45 C.F.R. Part 46 Subpart C). Although Exemptions 1 and 3-6 apply to research involving children (see 45 C.F.R. Part 46 Subpart D), Exemption 2 can only be used for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

e. List any collaborating sites where human subjects research will be performed and describe the role of those sites in performing the proposed research.

2. Sources of Materials:

a. Describe the research material obtained from living human subjects in the form of specimens, records, or data.

b. Describe any data that will be recorded on the human subjects involved in the project.

c. Describe the linkages to subjects, and indicate who will have access to subject identities.

d. Provide information about when the specimens, records, or data were collected and whether new material or data will need to be collected specifically for your proposed research project.

3. Justification for Exemption:

a. Indicate that you are claiming Exemption 4.

b. Provide a justification for why your research meets the criteria for Exemption 4.

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

What types of research meet the criteria for Exemption 4? Research projects involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. Determining the appropriateness of Exemption 4 for research using specimens and data can be complex.

Note: Prospective collection of additional specimens does not meet the criteria for Exemption 4.

If you are uncertain as to whether your research meets the criteria for Exemption 4, refer to Exemption 4 Guidance and Information.

If you need to consider an alternative scenario, return to the Decision Table.

SCENARIO C: HUMAN SUBJECTS RESEARCH CLAIMING EXEMPTION 1,2,3,5, OR 6

Criteria:

Human Subjects Research	Yes
Exemption Claimed	1, 2, 3, 5, 6
Clinical Research	Yes
Clinical Trial	N/A
NIH-Defined Phase III Clinical Trial	N/A

Instructions and Required Information:

Although no specific page limitation applies to this section of the application, be succinct.

Check the box marked “Yes” for item 4 on the Face Page, check the box marked “Yes” for item 4a on the Face Page, enter the exemption number that you are claiming. Enter “NA” for item 4b, since no OHRP assurance number is needed for exempt research.

Although your research may be exempt from the IRB oversight provisions, it is still human subjects research, and you need to follow the instructions that are identified for each of the following topics and provide the information that is requested.

In your application narrative, create a heading entitled “E. Human Subjects Research” and place it immediately after the last entry in the Research Design and Methods section. Address the following items in this new section. Include the following statement below the heading: “This Human Subjects Research falls under Exemption(s) … .”

1. Human Subjects Involvement and Characteristics:

a. Describe the proposed involvement of human subjects in the work outlined in the Research Design and Methods section.

b. Describe the characteristics of the subject population, including their anticipated number, age range, and health status.

c. Identify the criteria for inclusion or exclusion of any subpopulation (e.g., men, women, children).

d. Explain the rationale for the involvement of vulnerable populations, such as fetuses, neonates, pregnant women, children, institutionalized individuals. Please note that research involving prisoners is not exempt under any category (see 45 C.F.R. 46 Subpart C).

e. List any collaborating sites where human subjects research will be performed and describe the role of those sites in performing the proposed research.

2. Sources of Materials:

a. Describe the sources of the research material obtained from living human subjects in the form of specimens, records, or data.

b. Describe any data that will be recorded on the human subjects involved in the project.

c. Describe the linkages to subjects and indicate who will have access to subject identities.

d. Provide information about when the specimens, records, or data were collected and whether new material or data will need to be collected specifically for your proposed research project.

3. Justification for Exemption(s)

In this section, identify which exemption(s) (1, 2, 3, 5, or 6) you are claiming. (If you are claiming Exemption 4 please refer to Scenario B and the appropriate instructions.) Justify why your research is appropriate for the exemption(s) that you have claimed.

4. Inclusion of Women and Minorities (click and follow instructions)

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study.

Create a section entitled “Inclusion of Women and Minorities” and place it immediately following the last entry in the “Human Subjects Research” section.

Describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants. See http://grants.nih.gov/grants/funding/women_min/women_min.htm.

Include the Targeted/Planned Enrollment Table (MS Word or PDF) here.

5. Inclusion of Children (click and follow instructions)

For the purpose of implementing these guidelines, a child is defined as an individual under the age of 21 years. (For additional information see http://grants.nih.gov/grants/funding/children/children.htm and http://grants.nih.gov/grants/guide/notice-files/not98-024.html.)

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

If you are uncertain as to whether your research meets the criteria for an exemption please read: Question 2: Does your proposed human subjects research meet the criteria for one or more of the exemptions in the HHS regulations?

If you need to consider an alternative Scenario, return to the Decision Table.

SCENARIO D: CLINICAL RESEARCH

Criteria

Human Subjects Research	Yes
Exemption	No
Clinical Research	Yes
Clinical Trial	No
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information:

Although no specific page limitation applies to this section of the application, be succinct.

Check the box marked “Yes” for item 4 on the Face Page, for item 4a check the box marked “No,” and for item 4b enter your OHRP assurance number in the space provided on the Face Page.

In your application narrative, create a section entitled “E. Human Subjects Research” immediately following the last entry in the Research Design and Methods section. Include the following statement below the heading: “This Human Subjects Research meets the definition of ‘Clinical Research.’”

Create a subheading for each of the following items, follow the instructions that are identified for each topic, and provide the information that is requested:

- ***Protection of Human Subjects*** (click and follow instructions)
- ***Inclusion of Women and Minorities*** (click and follow instructions)
  Targeted/Planned Enrollment Table (MS Word or PDF)
- ***Inclusion of Children*** (click and follow instructions)

If your application involves collaborating sites, provide the information identified above for each participating site.

Guidance and Additional Instructions

Research that meets the criteria for Exemption 4 is not considered clinical research.

Research that uses *existing (archived)* specimens or data that *can* be linked to living individuals must address the inclusion of women, minorities and children as identified above, unless the investigator does not have access to the information. The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

If you are uncertain as to whether your research meets the criteria for clinical research, read: Question 3: Does your proposed research meet the definition of Clinical Research?

If you need to consider an alternative scenario, return to the Decision Table.

SCENARIO E. CLINICAL TRIALS

Criteria

Human Subjects Research	Yes
Exemption	No
Clinical Research	Yes
Clinical Trial	Yes
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information:

Check the box marked “Yes” for item 4 on the Face Page, for item 4a check the box marked “No,” and for item 4b enter your OHRP assurance number in the space provided.

In your application narrative, create a section entitled “E. Human Subjects Research” immediately following the last entry in the Research Design and Methods section. Include the following statement below the heading: “This Human Subjects Research meets the definition of a clinical trial.” Create a subheading for each of the following items, follow the instructions that are identified for each topic, and provide the information that is requested:

- ***Protection of Human Subjects*** (click and follow instructions)
- ***Data and Safety Monitoring Plan*** (click and follow instructions)
- ***Inclusion of Women and Minorities*** (click and follow instructions)
  Targeted/Planned Enrollment Table (MS Word or PDF)
- ***Inclusion of Children*** (click and follow instructions)

If your application involves collaborating sites, provide information for each of the issues identified above for each participating site.

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research. If you are uncertain as to whether your research includes a clinical trial please read: Question 4: Does your proposed research include a clinical trial? If you need to consider an alternative scenario, return to the Decision Table.

SCENARIO F. NIH-DEFINED PHASE III CLINICAL TRIAL

Criteria

Human Subjects Research:	Yes
Exempt:	No
Clinical Research:	Yes
Clinical Trial:	Yes
NIH-Defined Phase III Clinical Trial:	Yes

Instructions and Required Information:

Check the box marked "Yes" for item 4 on the Face Page, for item 4a check the box marked "No," and for item 4b enter your OHRP assurance number in the space provided.

In your application narrative, create a section entitled "E. Human Subjects Research" immediately following the last entry in the Research Design and Methods section. Include the following statement below the heading: "This Human Subjects Research is an NIH-Defined Phase III Clinical Trial."

Follow the instructions that are identified for each of the following topics and provide the information that is requested:

- ***Protection of Human Subjects*** (click and follow instructions)
- ***Data and Safety Monitoring Plan*** (click and follow instructions)
- ***Inclusion of Women and Minorities*** (click and follow instructions)
  Targeted/Planned Enrollment Table (MS Word or PDF)
- ***Inclusion of Children*** (click and follow instructions)

If your application involves collaborating sites, provide the information identified above for each participating site.

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research. If you are uncertain as to whether your research includes clinical research, read Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

If you need to consider an alternative scenario, return to the Decision Table.

HUMAN SUBJECTS RESEARCH POLICY

Human Subjects Research Policy includes federal regulations for the protection of human subjects and the following NIH policies related to human subjects research.

PROTECTION OF HUMAN SUBJECTS

The Department of Health and Human Services (HHS) regulations for the protection of human subjects provide a systematic means, based on established, internationally recognized ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the HHS. The regulations stipulate that an applicant organization, whether domestic or foreign, bears responsibility for safeguarding the rights and welfare of human subjects in HHS-supported research activities. The regulations require that applicant organizations proposing to involve human subjects in nonexempt research, provide written Assurance of Compliance with the Office for Human Research Protections (OHRP), that they will comply with requirements set forth in the HHS regulations to protect human subjects. These regulations, 45 C.F.R. 46, Protection of Human Subjects, are available from OHRP, Department of Health and Human Services, The Tower Building, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852 or by contacting OHRP at ohrp@osophs.dhhs.gov, Telephone: 1-866-447-4777 or (301) 496-7005.

Under HHS regulations to protect human subjects from research risks, certain research areas are exempt. However, if an applicant makes inappropriate designations of the noninvolvement of human subjects or of exempt categories of research, this may result in delays in the review of an application or the return of the application without review. The PHS will make a final determination as to whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the Research Plan. When in doubt, consult with the Office for Human Research Protections (OHRP), Department of Health and Human Services by accessing their website http://www.hhs.gov/ohrp for guidance and further information.

No non-exempt research involving human subjects can be conducted under a HHS award unless that organization is operating in accord with an approved Assurance of Compliance and provides verification that an Institutional Review Board (IRB) that is registered under the specific Assurance has reviewed and approved the proposed activity in accordance with the HHS regulations. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the HHS regulations. Foreign applicant organizations must also comply with the provisions of the regulations.

In addition to the HHS human subjects regulations, FDA regulations (21 C.F.R. part 50; 21 C.F.R. part 56) may also apply to your research. FDA regulations generally apply to biomedical research involving an unapproved drug, device or biologic and may apply to certain studies of approved products. Researchers proposing such research should consult with their IRB and the FDA to determine whether and how the FDA regulations may apply. Additional information on FDA regulations is available at (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm).

Studies that involve the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human research participants (known as “human gene transfer” or “gene therapy”) are subject to the oversight and biosafety requirements outlined in the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) when these studies are conducted at, or sponsored by, an institution that receives any NIH support for recombinant DNA research. These requirements, which include review by an Institutional Biosafety Committee and submission to the NIH for review by the Recombinant DNA Advisory Committee, are described in Section III-C-1 and Appendix M of the NIH Guidelines (accessible at: http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html). Additional information on the special requirements that pertain to human gene transfer can be found in a series of Frequently Asked Questions at: http://www4.od.nih.gov/oba/RAC/RAC_FAQs.htm.

Federal requirements to protect human subjects apply to most research on human specimens (such as cells, blood, and urine), residual diagnostic specimens and medical information. Research involving the collection or study of existing data, documents, records, pathological specimens, diagnostic specimens, or tissues that are individually identifiable is considered “research involving human subjects.” The NIH Office of Extramural Research Human Subjects website contains additional information and Frequently Asked Questions that is available to help

investigators understand how these federal requirements apply to their research. See http://grants.nih.gov/grants/policy/hs/index.htm.

The HHS regulations also require "Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency" (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.120). This independent evaluation is conducted at the NIH through the peer review system and NIH staff review, and, as required, will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. On the basis of this evaluation, the NIH may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

VULNERABLE POPULATIONS

Investigators who conduct research involving pregnant women, human fetuses and neonates, prisoners, or children must follow the provisions of the regulations in Subparts B, C, and D of 45 C.F.R. Part 46, respectively, which describe the additional protections required for these populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins. Relevant information may be obtained at the OHRP website (http://www.hhs.gov/ohrp/policy/index.html).

REMINDER: HHS regulations at 45 C.F.R. Part 46, subpart C describe requirements for additional protections for research involving prisoners as subjects *or* individuals who become prisoners after the research has started. Refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/prisoner.htm for complete instructions.

Exemptions 1-6 do not apply to research involving prisoners or subjects who become prisoners (see Subpart C). Although Exemptions 1 and 3-6 apply to research involving children (see Subpart D), Exemption 2 can only be used for educational tests or research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

DATA AND SAFETY MONITORING PLANS FOR CLINICAL TRIALS

For each proposed clinical trial, NIH requires a data and safety monitoring plan that describes oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. A detailed data and safety monitoring plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects. The reporting of Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other required entities. This policy requirement is in addition to any monitoring requirements imposed by 45 C.F.R. Part 46. NIH requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials.

RESEARCH ON TRANSPLANTATION OF HUMAN FETAL TISSUE

In signing the application Face Page, the duly authorized representative of the applicant organization certifies that if research on the transplantation of human fetal tissue is conducted, the applicant organization will make available, for audit by the Secretary, HHS, the physician statements and informed consents required by section 498A (b)(2) and (c) of the Public Health Service Act, 42 U.S.C. 289g (b)(2) and (c), or ensure HHS access to those records, if maintained by an entity other than the applicant organization.

RESEARCH USING HUMAN EMBRYONIC STEM CELLS

http://stemcells.nih.gov/index.asp

In signing the application Face Page, the duly authorized representative of the applicant organization certifies that if research using human embryonic stem cells is proposed, the applicant organization will be in compliance with the "Notice of Extended Receipt Date and Supplemental Information Guidance for Applications Requesting

Funding that Proposes Research with Human Embryonic Stem Cells" (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-006.html).

IRB APPROVAL

NIH does not require certification of IRB approval of the proposed research prior to NIH peer review of an application. See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-031.html.

Following NIH peer review, applicants and their institutions will be notified of the need for review and approval of the proposed research by an OHRP-registered IRB. See http://www.hhs.gov/ohrp to register an IRB. Documentation of IRB approval must be sent to the Grants Management Office identified in the notice requesting certification. This IRB certification must include: the PHS application number, title of the project, name of the principal investigator/program director, date of IRB approval, and appropriate signatures. You may also use the optional form "Protection of Human Subjects - Assurance Identification/IRB Certification/Declaration of Exemption (Common Rule) (OMB Form No. 0990-0263) to meet this requirement: http://www.hhs.gov/ohrp/humansubjects/assurance/OF310.rtf

An institution is automatically considered to be engaged in human subjects research when it receives an NIH award to support nonexempt human subjects research. All institutions engaged in human subjects research must obtain a Federal Wide Assurance (FWA) from OHRP. Instructions for applying for a Federal Wide Assurance (FWA) are available from the OHRP website at http://www.hhs.gov/ohrp/assurances/assurances_index.html.

Any modifications in the Research Plan section of the application, required by either NIH or by the IRB must be submitted with the follow-up certification of IRB approval to the NIH before the competing award is made. It is the responsibility of the principal investigator/program director and the applicant organization to submit the follow-up certification.

If more than year will have elapsed between the initial IRB review date and the anticipated award date, the awarding unit staff shall require re-review by the IRB prior to award.

REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

NIH requires education on the protection of human research participants for all individuals identified as Key Personnel before funds are awarded for applications or contract proposals involving human subjects. For information relating to this requirement, see the following see the following notices (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html), and Frequently Asked Questions found at: http://grants.nih.gov/grants/policy/hs_educ_faq.htm. Prior to award, applicants will be required to provide a description of education completed in the protection of human subjects for all Key Personnel involved in human subjects research. Although NIH does not endorse programs, there are curricula available that can provide guidance or that can be modified to provide training in this area. See http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp for computer-based training developed for NIH that can be downloaded at no charge. For information on facilitating education and developing curricula, see http://www.nih.gov/sigs/bioethics.

RELEVANT POLICIES AND INFORMATION

PROCEDURES FOR SUBMISSION OF COMPLIANCE DOCUMENTS TO THE HUMAN PLURIPOTENT STEM CELL REVIEW GROUP FOR THE RESEARCH USE OF HUMAN EMBRYONIC GERM CELLS	NOTICE: NOT-OD-02-049 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-049.html
GUIDANCE FOR INVESTIGATORS AND INSTITUTIONAL REVIEW BOARDS REGARDING RESEARCH INVOLVING HUMAN EMBRYONIC STEM CELLS, GERM CELLS AND STEM CELL-DERIVED TEST ARTICLES	NOTICE: NOT-OD-02-044 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-044.html

IMPLEMENTATION ISSUES FOR HUMAN EMBRYONIC STEM CELL RESEARCH - FREQUENTLY ASKED QUESTIONS	NOTICE: NOT-OD-02-014 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-014.html
FEDERAL GOVERNMENT CLEARANCES FOR RECEIPT OF INTERNATIONAL SHIPMENT OF HUMAN EMBRYONIC STEM CELLS	NOTICE: NOT-OD-02-013 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-013.html
NOTICE OF EXTENDED RECEIPT DATE AND SUPPLEMENTAL INFORMATION GUIDANCE FOR APPLICATIONS REQUESTING FUNDING THAT PROPOSES RESEARCH WITH HUMAN EMBRYONIC STEM CELLS	NOTICE: NOT-OD-02-006 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-006.html
NOTICE OF CRITERIA FOR FEDERAL FUNDING OF RESEARCH ON EXISTING HUMAN EMBRYONIC STEM CELLS AND ESTABLISHMENT OF NIH HUMAN EMBRYONIC STEM CELL REGISTRY	NOTICE: NOT-OD-02-005 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html
NIH FUNDING OF RESEARCH USING SPECIFIED EXISTING HUMAN EMBRYONIC STEM CELLS	NOTICE: NOT-OD-01-058 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-059.html

NIH POLICY ON THE INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, upon the recommendation of an Institute/Center Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subjects of all ages.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The research plan should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants. See http://grants.nih.gov/grants/funding/women_min/women_min.htm.

NIH POLICY ON INCLUSION OF CHILDREN

(See Definition of "child.")

Research involving children must comply with the NIH Policy and Guidelines on the Inclusion of Children in Clinical Research. The following excerpts provide the key policy statements. Investigators should obtain full copies of the Policy and Guidelines from NIH staff, or from the NIH grants Web site under http://grants.nih.gov/grants/funding/children/children.htm.

NIH policy requires that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH unless there are clear and compelling reasons not to include them. Therefore, proposals for clinical research must include a description of plans for including children. If children will be excluded from the research, the application or proposal must present an acceptable justification for the exclusion.

In addition, the involvement of children as subjects in research must be in compliance with all applicable subparts of 45 C.F.R. Part 46 as well as with other pertinent Federal laws and regulations.

Additionally, IRBs have special review requirements to protect the well-being of children who participate in research. These requirements relate to risk, benefit, parental/guardian consent, and assent by children, and to research involving children who are wards of the state or of another institution. The local IRB approves research that satisfies the conditions set forth in the regulations.

NIH POLICY ON REPORTING RACE AND ETHNICITY DATA: SUBJECTS IN CLINICAL RESEARCH

The Office of Management and Budget (OMB) (http://www.whitehouse.gov/omb/fedreg/ombdir15.html) defines minimum standards for maintaining, collecting and presenting data on race and ethnicity for all Federal reporting agencies (including NIH). The categories in this classification are social-political constructs and should not be interpreted as being anthropological in nature. The standards were revised in 1997 and now include two ethnic categories, "Hispanic or Latino" and "Not Hispanic or Latino." There are five racial categories: American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; and White. Reports of data on race and ethnicity shall use these categories. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. The following definitions apply to the minimum standards for the ethnic and racial categories.

Ethnic Categories:

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, “Spanish origin,” can be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino

Racial Categories:

American Indian or Alaska Native: A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American: A person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Ethnic/Racial Subpopulations: In addition to OMB ethnic and racial categories, NIH uses the following definition for ethnic/racial subpopulations:

Subpopulations: Each ethnic/racial group contains subpopulations that are delimited by geographic origins, national origins, and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific origins and/or cultural heritage. Attention to subpopulations also applies to individuals who self identify with more than one race. These ethnic/racial combinations may have biomedical, behavioral, and/or social-cultural implications related to the scientific question under study. (http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm)

GUIDANCE ON COLLECTING RACE AND ETHNICITY DATA FROM STUDY SUBJECTS

When an investigator is planning to collect data on ethnicity and race, the categories identified above should be used. The collection of greater detail is encouraged, for example on ethnic/racial subpopulations. However, any collection that uses more detail must be designed in a way that data can be aggregated into these minimally required categories. Use self-report or self-identification to collect this information by asking two separate

questions – one on ethnicity and one on race. Collect ethnicity information first followed by the question on race and provide subjects with the option to select more than one racial category. An example of a format for collecting information from study subjects in the US and that meets the OMB requirements can be found in the Ethnic Origin and Race section of the Personal Data Form Page (MS Word or PDF) in the PHS 398.

See NIH Policy on Inclusion of Women and Minorities.

Collecting Data on Foreign Populations: If you are conducting clinical research outside of the US, you should design culturally sensitive and appropriate data collection items and instruments that allow subjects to self-identify their ethnic and racial affiliation in a culturally appropriate manner. These items, however, should be designed in a way that allow you, the investigator, to aggregate the information into the OMB minimally required ethnic and racial categories when reporting the information to NIH.

Submitting Applications or Proposals Using Existing Data in Clinical Research with No Plans for Collecting New/Additional Data:

Investigators are instructed to provide plans for the total number of subjects proposed for the study and to provide the distribution by ethnic/racial categories and sex/gender. Under these circumstances, investigators are not required to re-contact subjects solely to comply with the newly revised categories. If the existing data on ethnicity and race allow accurate correspondence with the new categories, the investigator can use the format in the Targeted/Planned Enrollment table (MS Word or PDF). However, if the existing data do not allow accurate correspondence with the new categories, information may be reported using the former categories and according to the format in the 4/98 Version of the Inclusion Table
http://grants.nih.gov/grants/funding/women_min/InclusionOld_Form.pdf

Annual Progress Reports (Type 5 applications) and Competing Supplement Applications

In annual Progress Reports, investigators conducting clinical research are required to provide the cumulative total enrollment of subjects to-date, showing the distribution by ethnic/racial categories and sex/gender on EITHER the new Inclusion Enrollment Report (MS Word or PDF) OR the format in the former 4/98 Version of the Inclusion Table (MS Word or PDF).

For competing supplement applications, any proposed additions to the Targeted/Planned Enrollment Table should be provided, in addition to the current Inclusion Enrollment Table.

If Data Collection is Ongoing, Such that New Subjects Will be Enrolled and/or Additional Data Will be Collected from Human Subjects:

Investigators may choose to report ethnicity/race and sex/gender sample composition using EITHER the new Inclusion Enrollment Report (MS Word or PDF) OR the format in the former 4/98 Version of the Inclusion Table (MS Word or PDF).

[Note: If investigators with on-going data collection choose to report information using the new Inclusion Enrollment Report, they must continue to use this format for the remaining years of the project.]

If Data Collection is Complete, Such that No New/Additional Subject Contact is Planned:

Investigators may EITHER continue to report using the former categories and according to the 4/98 Version of the Inclusion Table, OR, if data allow accurate correspondence with the new categories, use the format in the new Inclusion Enrollment Report.

Additional Information

Additional information on NIH policy regarding the Inclusion of Women and Minorities in Clinical Research can be found at the website http://grants.nih.gov/grants/funding/women_min/women_min.htm.